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Some Recent Advances in the Chemistry of Fats*,†

By B. F. Daubert

The present war emergency has served to focus attention on the important role of fats and oils in our economy. It is, therefore, singularly gratifying to report an increasing scientific interest in problems peculiar to these natural products. Developments during the past several years have been a reflection of the widespread interest in their many possible industrial uses. While more than one-half of the approximately 12 billions of pounds produced in 1943 was consumed as food, industries have found use for the remaining total in the production of soaps, cosmetics, paints and varnishes, and a wide variety of miscellaneous products.

A characteristic feature of fats is their complexity. No longer can we conceive of a fat as consisting of glycerol and three fatty acids. Sufficient evidence has been accumulated to indicate that fats are complex mixtures of mixed triglycerides of which the constituent fatty acids are both saturated and unsaturated. Indeed, the realization of the large number of possible combinations of glycerides in a fat serves to emphasize their complexity. Inherent problems of the molecular structure of the component glycerides of a fat have been a worthy and exciting challenge to the chemist, and while considerable progress has been in evidence on a study of their compositions through the application of such techniques as fractional distillation, fractional crystallization, selective hydrogenation and chromatographic absorption, developments during the past several years have indicated a quickened pace in the fundamental chemical study of these naturally occurring products.

AUTOXIDATION AND ANTIOXIDANTS

The preservation of fats against deterioration has been long a major problem of the edible fat and oil industry, and attention, therefore, has been directed in recent years to the condition of rancidity. As Olcott and Mattill (1) have so aptly expressed, "a fat may be described as rancid when it contains enough oxidation products or free short-chain fatty acids to provide organoleptic evidence of their presence." The condition of rancidity, caused mainly by atmospheric oxidation, is undesirable in a fat not only because of objectionable odors and tastes but because it promotes the destruction of vitamins A (2), D (3), E (4) and members of the B-complex (5) and partially destroys the essential fatty acids (6).

Since oxidation is the major cause of ran-

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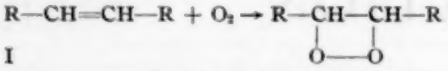
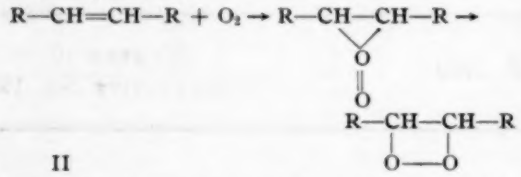
cidity, it may not be inappropriate to discuss briefly some of the postulated mechanisms of this autoxidation. The classical concepts of the reactions that occur during oxidative rancidity involve the addition of oxygen to an unsaturated carbon to carbon linkage and the subsequent formation of a peroxide (7, 8):



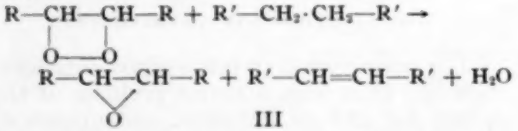
I

Staudinger (9) believes that a highly reactive moloxide stage precedes the formation of the peroxide:



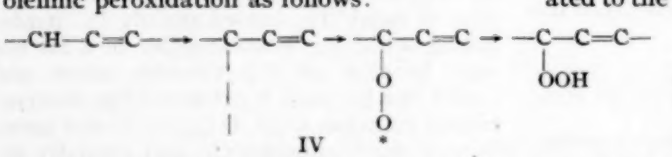
II

The active peroxide once formed presumably undergoes rapid decomposition with the simultaneous formation of new peroxide molecules. Several mechanisms have been postulated for the decomposition of these organic peroxides and the initiation of a chain of reactions accompanying the development of oxidative rancidity. These secondary reactions give rise to degradation products that provide qualitative indications, at least, of reaction paths. Powick (10), who has extensively investigated autoxidation reactions, suggested that the peroxide reacted with a saturated fatty acid chain by a process of dehydrogenation with the corresponding formation of a new double bond. The double bond would then be able to peroxidize and subsequently decompose into short-chain saturated aldehydes and acids:



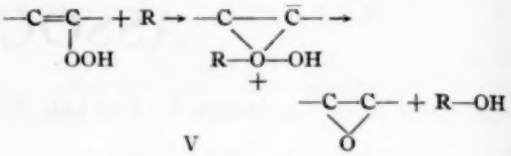
III

Farmer, *et al.* (11, 12, 13), have recently postulated a hydroperoxide as the first compound formed in the autoxidation of olefinic type substrates (*e. g.*, unsaturated fatty acids). This hydroperoxide is formed presumably by a free radical mechanism of olefinic peroxidation as follows:



IV

Evidence in support of this mechanism was obtained by the isolation of a rather pure hydroperoxide of cyclohexene and methyl oleate, and by the fact that the rate of loss of total unsaturation failed to parallel the rate of oxygen absorption by the substrate. These investigators indicated possible decomposition stages for the hydroperoxide as follows:



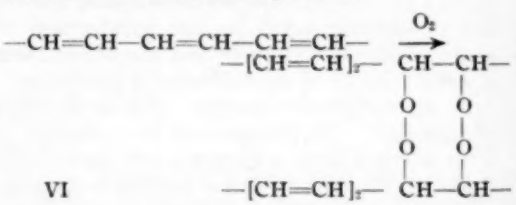
V

It would seem on the basis of Farmer's work that it should be possible to isolate a trihydroxystearic acid from the oxidation products of oleic acid. This has not been done so far as the author is aware.

Atherton and Hilditch (14) have recently studied the union of gaseous oxygen with methyl oleate at 20° and 120° and confirm the view of Farmer that the autoxidation of methyl oleate at 20° involves the conversion of the methylene group at carbon atom 8 or 11 of the acyl chain into a hydroperoxide. Autoxidation of the methyl oleate, however, at the higher temperature, appeared to proceed exclusively at the double bond followed by secondary reactions at other points in the aliphatic chain. There was little evidence for the presence of hydroperoxide.

Triebs (15), in a recent study of the effect of dilution on the autoxidation of eleostearic acid and ricinoleic acid esters, has obtained results which suggest the following mechanism of autoxidation:

(*a*) Dimerization of chains by oxygen addition in undiluted systems:



VI

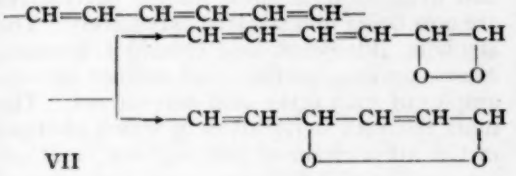
(*b*) Increasing dilution prevents dimerization and favors the 1,2- or 1,4- addition of oxygen, as shown in equation VII.

(*c*) The peroxidic 1,4- addition product is rearranged to 1,4- enol which is hydrogenated to the 1,4- glycol. (See equation VIII.)

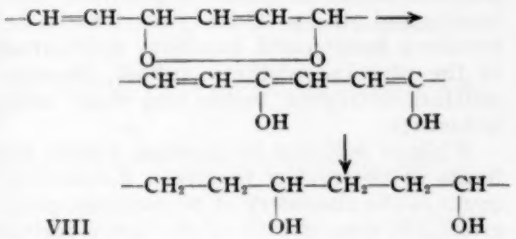
(*d*) The 1,2- addition product is split under formation of aldehydes, as shown in equation IX.

Polymerization reactions may also occur in addition to the possible decompositions of fats to ketones, aldehydes, etc. While the mechanisms of

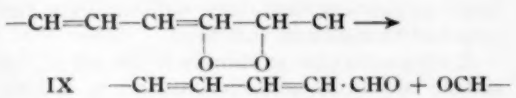
polymerization reactions in the autoxidation of fats have received attention recently, consideration of this phase of autoxidation is beyond the scope of this review.



VII



VIII



IX —CH=CH—CH=CH·CHO + OCH—

In parallel with recent research on the mechanisms of the autoxidation of fats, investigations on antioxygenesis particularly as related to edible fats and oils have occupied the attention of many investigators. Substances that retard the oxidation of fats are usually referred to as "antioxidants." Many of these materials are present in naturally occurring fats and their presence explains the preferential stability or resistance of such oils as sweet almond, sesame and others to oxidation, particularly when compared to other vegetable and animal fats of similar unsaturation.

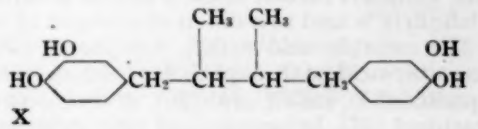
The resistance of a fat or oil to autoxidation is measured in units of time under specified conditions. This period of resistance is known as the induction period and is a measure of the stability of a fat or oil. The role of the antioxidant in stabilizing fats by prolonging the induction period seems to be related to the ability of the antioxidant to combine with the active peroxide molecules.

Many phenolic substances have the ability at relatively low concentrations to inhibit the autoxidation of fats. In general, the most effective phenols are those which have some type of oxygen linkage in the *ortho* and *para* position or both to the hydroxyl groups. Compounds of this nature, particularly the quinones and the tocopherols, have been extensively studied for their antioxidant properties. Taufel, *et al.* (16), indicate the order of antioxygenic activity of the quinones to be

quinone > hydroquinone > quinhydrone

Golumbic (17) has studied the kinetics of the oxidation of tocopherol during the induction period of animal and vegetable fats photometrically. Using ethyl esters of lard fatty acids tocoquinones appeared as the intermediate oxidation products of the tocopherols. Chroman-5,6- quinones developed from oxidation of their precursors which are found in animal but not in vegetable fats. These *ortho* quinones retarded active oxygen formation in vegetable oils after the disappearance of the tocopherols. Calkins and Mattill (18) in measuring the absolute rate of oxidation of ascorbic acid in the ethyl esters of lard fatty acids, in the presence and absence of quinone, conclude that the real antioxidant is an oxidation product of ascorbic acid. These investigators make the interpretation that the quinone acts as a catalyst primarily for the reason that at any time during the induction period the original amount of quinone could be recovered. The catalytic action of the quinone apparently consists of a reduction to a semiquinone which subsequently is oxidized back to quinone by a peroxide radical.

Nordihydroguaiaretic acid (19), recently isolated from a common desert bush (creosote bush) and frequently referred to as NDGA, has shown excellent promise as an antioxidant. The molecular structure of the chemical is indicated as follows:



X

Nordihydroguaiaretic acid compares favorably with other substances of the phenolic type in antioxygenic activity (20). In the presence of ascorbic acid its antioxidant properties in fats are enhanced. The use of this substance in lard and rendered pork fat has been approved.

Gum guaiac, an excellent stabilizer and innocuous physiologically, has been found by Mitchell and Black (21) to be an effective antioxidant for lard. This naturally occurring gum resin had been reported previously as possessing antioxygenic properties, presumably due to the presence of guaiaretic acid (22).

Other substances recently found to possess antioxidant activity are maleic acid, fumaric acid and their esters (23, 24). Thiourea and sulfhydryl compounds proved to

be effective with fats in the presence of water (25). Riemenschneider, *et al.* (26), found that fatty acid monoesters of *l*-ascorbic and *d*-isoascorbic acids increased the stability of prime steam lard to a level comparable to hydrogenated vegetable shortening. In general, they found that the monoesters were somewhat more effective with vegetable oils than with lard. This difference may be attributed to the synergistic effect of the natural inhibitors present in vegetable oils.

Boehm and Williams (27), in a study of methods of preventing rancidity due to autoxidation in oils and fats to be used in pharmaceutical preparations, found *n*-propyl gallate to be an excellent antioxidant. It prevented rancidity in fats of both animal and vegetable origin. Preliminary texts have indicated unlimited applicability in pharmaceutical preparations.

Several very excellent analytical methods for the quantitative determination of antioxidants added to edible fats have been described recently (28, 29, 30). These methods make possible future studies on the rate of loss of antioxidants because of autoxidation.

The extraordinary efforts of research investigators to find satisfactory antioxidants applicable to the edible oil and fat industry and the pharmaceutical field are reflected in the number of patents issued within the past several years. Antioxidants patented within the past year include coffee oil (31), peroxides of fatty acids derived from cocoa butter (32), Schiff base compounds in which the carbonyl carbon of each ketone group is definitely bound to a different nitrogen atom (33), ascorbic acid with a tocopherol (34), ascorbic acid with naphthols, quinones and quinols (35), caffeic acid (36), acetyl methyl carbinol (37), hexuronic acid with quinones, hydroquinones, naphthols and chromans (38), phosphatides with polyhydroxybenzene (39).

FATTY ACID DERIVATIVES AND SYNTHETIC GLYCERIDES

Within the past decade the possibilities of creating new and useful products from high molecular weight fatty acids have opened up entirely new fields of chemical research. The economical preparation of fatty acid derivatives in large bulk has been largely the result of the development of efficient fractional distillation methods in the preparation of the fatty acid intermediates of a satisfactory degree of purity. Fatty acids of a purity of 90 per cent or better are now produced in large volume at reasonable cost. As a natural consequence of the availability of such acids a large number of simple derivatives have been prepared from them in which changes in the carboxyl group have been involved. The properties and utilization of these simple derivatives are now being investigated extensively. The alcohols, aldehydes, acid chlorides, ketones, esters, amides, nitriles and amines are examples of such fatty acid derivatives. The more complex derivatives in which changes in the alkyl chain of the aliphatic acid are involved are the hydroxy acids, halogenated addition products, synthetic polymers, elastomers and others. Both types of these derivatives have found extensive application in the plastics, synthetic rubber, pharmaceutical, detergent, textile and many other industries.

While it will not be possible within the limits of the review to give a detailed account of the chemistry of preparation, properties and uses of each of the many derivatives, a brief discussion, perhaps, of those more important certainly will indicate the trend of research in this field.

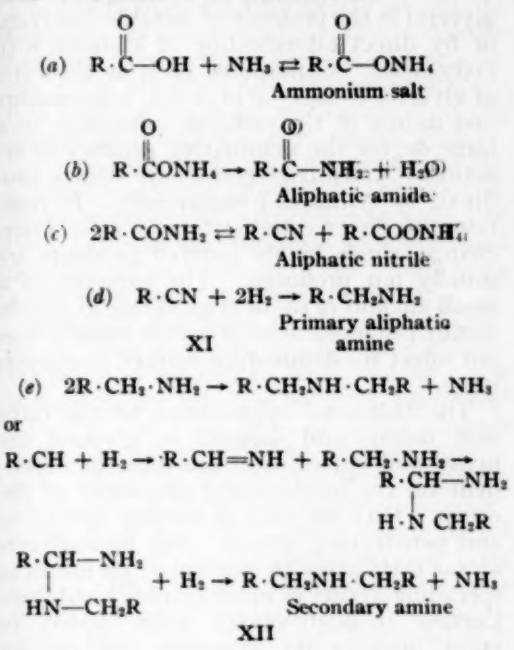
A characteristic in common for all of the simple aliphatic acid derivatives is a long hydrocarbon chain attached to a polar group. This fact, in most instances, gives rise to their interesting surface characteristics.

Probably the most interesting of this class of compounds is the group of nitrogen derivatives. This group includes the nitriles, amines and amides. All of these compounds have found extensive application as emulsifying and wetting agents, flotation and water-treating agents, plasticizing agents in plastics and in textile finishing processes. Furthermore, the amines possess bactericidal properties and have also been used as insecticides, and the amides because of their relatively high melting points are very useful as chemical intermediates, waterproofing agents and protective coatings. Ralston and Barrett (40) have found that aliphatic nitriles containing from ten to fourteen carbon atoms possess high repellent activity against insects. Lauronitrile, in particular, was found to be nontoxic to humans both internally and externally. Ralston (41) also found that dioctyl amine possessed an exceptionally high killing power for insects. He suggested that it may be considered as a possible substitute for pyrethrum.

According to Ralston (42), the most probable reactions for the preparation of aliphatic acid amines may be represented as indicated in XI.

In (*d*) the conditions of hydrogenation determine to a large extent the nature of the

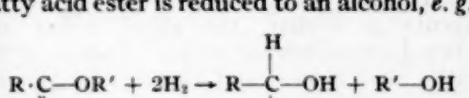
products of reaction, *i. e.*, secondary amines may be produced as in XII (43).



XI

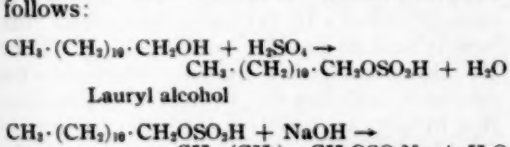
XII

The reduction of glycerides or other esters of fatty acids to alcohols of high molecular weights has been known for a long time. Recent investigations of these reactions have emphasized their industrial importance. By the process of hydrogenation using a specific catalyst the carboxyl group of the fatty acid ester is reduced to an alcohol, *e. g.*:



XIII

Sulfates of these alcohols may then be produced by reaction with sulfuric acid as follows:

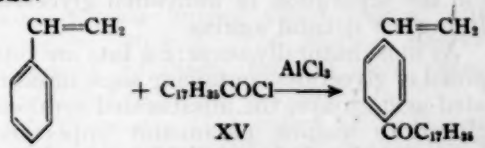


XIV

The sulfated alcohols prepared from the higher molecular weight aliphatic acids have found extensive use in the detergent and textile processing industry (44). In fact, it was because of the search for new detergent and wetting agents that the unusual properties of the sodium salts of the acid sulfates of alcohols were noted. The unsaturated oleyl and linoleyl alcohol when produced in commercial quantities should find extensive application in the field of cosmetics.

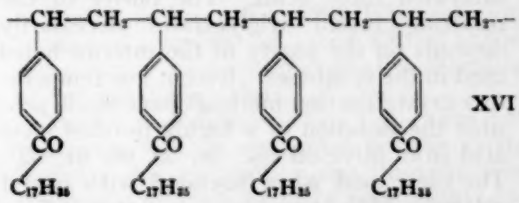
A group of aliphatic acid derivatives for which excellent industrial promise is held are the ketones. The dialkyl type of ketone, *e. g.*, diundecyl ketone (laurone), is prepared by the catalytic decarboxylation of the corresponding acid. These compounds already have been used as dielectric materials, plasticizers, waterproofing agents and wax substitutes.

Saturated aliphatic acid chlorides have been used to prepare a host of synthetic derivatives and many of them for a long time have found extensive use as acylating agents in synthetic organic chemistry. The plastics industry has successfully utilized materials produced by the introduction of long acyl groups by means of acid chlorides into monomeric molecules and subsequent polymerization. The presence of these groups in resins increases their flexibility and since there is great need for more flexible resins extensive use of this type of product is indicated (45). As a case in point, monomeric styrene polymerizes by addition polymerization to high polymeric resins of a molecular weight typical of reaction conditions. These resins can be made transparent and more flexible by first acylating the styrene with a high molecular weight aliphatic acyl chloride:



XV

Polymerization of the *p*-stearoyl styrene by peroxide catalysis yields a high molecular weight flexible resin of the following probable structure:



XVI

The unsaturated acid chlorides of oleic, linoleic and linolenic acids recently prepared (46) by reaction of the corresponding acid and oxalyl chloride should find extensive application in the preparation of resins of a wide variety of properties. Not only will the resins have the properties of the polymerized monomers, but also those of the drying oil acids. In fact, industrial uses of aliphatic acid derivatives are almost limitless.

During the past two decades reliable methods of synthesis for glycerides have been well established and while the almost infallible methods themselves have been excellently discussed in recent reviews (47,48, 49, 50), it may not be inappropriate to repeat the fundamental purpose of preparing these compounds. In essence, the purpose of synthesis is to provide knowledge of the molecular structure of fats far too complex for resolution into their simpler components by present analytical means. The isolation of individual glycerides from relatively few simple fats has been accomplished but the assignment of a definite configuration has been somewhat uncertain. Greater assurance of the structure and configuration of glycerides isolated from natural sources can be obtained by comparing their physical and chemical properties with those prepared by reliable synthetic methods.

The glycerides synthesized in the research laboratory are highly purified products and are prepared, in most instances, utilizing highly purified fatty acid chlorides. Such characteristics of these products as heat of combustion (51), polymorphism (52), X-ray diffraction patterns (53) and other physical properties not only serve as reference data for the identification of isolated natural glycerides but provide information which aids in the development of better methods for the separation of individual glycerides from their natural sources.

As most naturally occurring fats are composed of glycerides containing some unsaturated acid groups, the unsaturated synthetic glycerides assume paramount importance in any study of glyceride mixtures. It has been shown by recent investigations (54, 55, 56) that the prevailing methods of synthesis can be adapted to glycerides containing unsaturated fatty acids. The purity of the resulting mixed triglycerides necessarily depends on the purity of the intermediates used in the syntheses. Recent low temperature crystallization methods have made possible the isolation of a highly purified oleic acid from olive oil (57, 58, 59, 60, 61, 62). The oleic acid when acylated with oxalyl chloride (46) provides an intermediate which, when reacted with a saturated mono- or diglyceride of a saturated fatty acid, produces a highly satisfactory product. Several series of symmetrical and unsymmetrical mixed triglycerides containing both one and two oleic acid groups have been prepared recently and their physical and chemical behavior studied.

Numerous important industrial uses have developed from the laboratory synthesis of glycerides. Technically, however, both mono- and diglycerides are produced usually by ester interchange on heating fats and glycerol in the presence of suitable catalysts, or by direct esterification of glycerol with fatty acids. Conditions, such as the ratio of glycerol to fatty acid or fat, temperature and nature of the catalyst, determine to a large degree the dominating product of reaction. Mixed triglycerides are seldom produced by synthesis commercially. In reactions by direct esterification or ester interchange, single highly purified products are usually not produced. The presence of a small amount of di- or triglyceride in a technically produced monoglyceride usually does not affect its dominating surface characteristics.

The industrial applications of the fatty acid mono- and diesters of glycerol are many and varied, and are directly dependent on the fundamental properties of the esters. They are used as wetting, spreading and penetrating agents. The monoglycerides of fatty acids, in particular, are useful as spreading agents in photographic emulsions. Certain monoglycerides when added to yeast improve its wrapping and cutting quality and improve its whiteness. The esters are used to form coatings on hygroscopic solids, such as bile salts and liver concentrates and when added to shortenings or margarine considerably reduce spattering during frying. Since these esters dissolve or blend with both natural and synthetic resins they serve as effective plasticizing agents in shellac, the alkyd resins and phenol-formaldehyde resins. Certain of the fatty acid mono- and diesters of glycerol when added to pastries and other baked products improve their quality. They are excellent stabilizers for water-in-oil emulsions and are useful as emulsifiers in cosmetics and tooth pastes and improve the whipping quality of cream. The addition of monoglycerides to synthetic butadiene rubbers is said to prevent sun-checking. They are also used as low-freezing lubricants for precision instruments, to inhibit crystallization in fatty materials, as vehicles for water-soluble dyes, and as agents to improve the consistency of lubricating oils. While these are but a few of the more recent applications of the fatty acid esters of glycerol there is no doubt but that many new uses will be found for these synthetic products.

ANALYTICAL METHODS

The measurement of absorption spectra for fatty acids in the far region of the ultraviolet has resulted in the development of methods for the quantitative calculation of

the fatty acids with two or more double bonds present in a fat.

It has been recognized clearly as early as 1868 that organic compounds of a particular structure had certain spectral characteristics. The intensity and position of absorption bands of ethylenic and carboxyl groups depend upon their number, position with respect to each other and the nature of the substituent groups attached to the unsaturated carbon atoms. Since the inception of these fundamental concepts spectrographic data for natural fats and their mixed fatty acids have been extensively studied.

Spectral methods, therefore, have recently been employed to determine quantitatively the linoleic, linolenic and, in a few instances, the arachadonic acid content of fats. The method is based upon Moore's (63) observation that the spectral absorption of fatty acids increased with increasing unsaturation. This investigator also observed that prolonged heating of fats during saponification caused nonconjugated fatty acids to become conjugated and thereby to absorb radiation in the ultraviolet region. While Kass, *et al.* (64), and Miller and Burr (65) had reported the possibilities of a quantitative measurement by spectral absorption of the linoleic acid content of vegetable oils by alkali isomerization, Mitchell, *et al.* (66, 67), extended and refined the method so that it now has wide applicability.

The method is more rapid and direct than Kaufman's Thiocyanogen method for the determination of the oleic, linoleic and linolenic acid content of a fat. The latter method, which depends on the determination of the iodine value, thiocyanogen number and the saturated fatty acid content of a fat, has, in the past, been somewhat unreliable and unless conditions are carefully controlled still leaves much to be desired. The spectrophotometric method, in essence, involves the heating of a fat or fatty acids in alkaline ethylene glycol for a period of thirty minutes at 180°, and after quick cooling the isomerized soaps are diluted with carefully purified 99 per cent alcohol and the absorption of the diluted samples measured in a photoelectric spectrophotometer. A blank solution, including dilutions, must be observed through the entire procedure. When the value $E^{1\%}_{1\ cm.}$ is plotted against wave length, typical absorption peaks result at 2340 Å. and 2680 Å. if both linoleic and linolenic acids are present.

Comparison with standard values on the isomerized pure acids provides a method of calculating the per cent of the two acids present in the original sample. For complete information on the method of calculation the reader is referred to the excellent article by Mitchell, Kraybill and Zscheile (66). Investigators in this laboratory have preferred to use triple distilled water for the diluting solvent in place of ethanol because it is more easily prepared and gives more consistent results.

Combined with such analytical data as iodine values and saponification equivalents of the ester fractions of fats obtained by fractional distillation, the spectrophotometric method makes possible a complete direct analysis of fats containing saturated acids, oleic, linoleic and linolenic acids.

Other improvements in analytical methods the past year of interest to the pharmaceutical reader are those concerning iodine values and saponification numbers. In the determination of iodine values Jasperson (68) included the use of mercuric acetate as a reaction catalyst and applied it to the bromometric method.

Norris and Bushwell (69) improved the rapidity of both the Wijs and Hanus methods but found the Hanus procedure, using mercuric acetate as a catalyst, was unsuccessful with conjugated fats and castor oil.

Rieman (70) determined the saponification numbers of various fats and eliminated the blank by the use of double indicators. First, excess caustic was titrated to a phenolphthalein indicator change, and by adding bromothymol blue and 10 cc. of benzene the soap formed during saponification could then be titrated. The method checked standard methods for all oils except acetylated castor oil and palm oil.

A procedure (71) called the "Woburn Iodine Absorption Method" makes use of iodine bromide in 1.6 to 2 times the concentration of Hanus solution for determining total unsaturation in fats. The differential between the iodine value by this method and a partial iodine value with Wijs solution limited to a two-minute contact time, at the temperature of ice, compared well with maleic anhydride diene values.

Mattil and Longenecker (72) have recently shown that a linear relationship exists between the composition and the refractive index of a mixture of fatty acid methyl esters. This relationship makes available an additional analytical method for the calculation of the composition of unknown mixtures of methyl esters.

The advances in the chemistry of fats have been rapid during the past decade, and this discussion, while in nowise complete, has served to indicate the trend of research. Greater advances will necessarily follow as research chemists become more interested in this interesting field of chemical research.

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Isotonic Solutions. II. The Permeability of Red Corpuscles to Various Substances*,†

By William J. Husa‡ and James R. Adams

In a previous paper, Husa and Rossi (1) discussed the advantages and limitations of various methods for calculating the concentration of isotonic solutions and presented new experimental data on the freezing points of solutions of a number of drugs.

The purpose of the present investigation was to study certain aspects of isotonic solutions as prepared by pharmacists for use in medical practice. Research was conducted on the technique and applicability of freezing-point methods, and the results were correlated with calculations by the osmotic factor method and with the results of hemolytic tests. Particular attention was devoted to the hemolytic method, since this method has certain advantages which apparently have been overlooked by most previous investigators in this field.

EXPERIMENTAL

Freezing-Point Methods.—Comparative tests were made with the Beckmann and Bartley freezing-point methods. The Beckmann apparatus employed was of the usual type. The Bartley apparatus differs from that of Beckmann in that an alcohol bath is used instead of an air bath, and instead of using a mixture of ice, water and salt, the freezing is brought about by aeration of ether in a vacuum tube.

The usual form of the Bartley apparatus (2) was used, except that the stirring was done manually instead of by means of a small motor. Intermittent stirring is sufficient until the temperature at which the solution freezes is reached. Then by rapid stirring, and by controlling the aeration of ether in the outer bath, the supercooling may be held to a minimum. The temperature falls below the freezing point of the solution, then rises suddenly to a maximum which is the freezing point of the solution, and remains there for several seconds.

In determining the freezing point of a solution, the tests were repeated until three consecutive readings varying not more than 0.01 degree were obtained. Each reading was made to an accuracy of 0.002 degree.

Hemolytic Method.—The blood used in the hemolytic method was obtained from the veins of the left arm of a human male, age thirty-eight years, by means of a hypodermic syringe. The blood was immediately defibrinated by gentle rotation in a flask with glass beads until the fibrin had separated; then the defibrinated blood was poured off. Quantities of 20 to 25 cc. were taken each time and stored in stoppered glass containers in a refrigerator. The blood was used from one to twenty-four hours after being taken.

One-tenth cubic centimeter of the fresh, defibrinated blood was added to 5 cc. of the solution to be tested, giving a dilution of 1 to 51, and mixed by gentle shaking. The mixture was allowed to stand for thirty minutes and then centrifuged for one minute. Hemolysis was indicated by a clear, red color of the mixture with no red sediment appearing in the bottom of the tube. Absence of hemolysis was indicated by a clear, colorless supernatant liquid with a red sediment (corpuscles).

Isotonic Solution of Dextrose and Sodium Chloride, N. F. VI.—Isotonic Solution of Dextrose and Sodium Chloride N. F. VI has the following formula: dextrose (monohydrated) 25 Gm., physiological solution of sodium chloride U. S. P. XI 500 cc., freshly distilled water, to make 1000 cc. Freezing-point determinations were made on the official solution as well as on solutions of the separate ingredients taken individually in double the concentration.

The results in Table I indicate that Isotonic Solution of Dextrose and Sodium Chloride N. F. VI is slightly hypotonic, since the commonly accepted freezing point of average blood is −0.56° C. However, the slight hypotonicity does not affect the use of the solution since the freezing point is well within the range of safety for such solutions. Solutions of dextrose and sodium chloride individually, taken in double the concentration in which they appear in the N. F. VI solution, are likewise slightly hypotonic.

Isotonic Solution of Dextrose and Sodium Chloride N. F. VI was also tested by the hemolytic method and it was found that the solution does not cause hemolysis.

Nasal Spray.—Tests were made on a nasal spray of the following formula:

Ephedrine hydrochloride	1.0 Gm.
Menthol	0.1 Gm.
Chlorobutanol	0.5 Gm.
Alcohol	1.67 cc.
Dextrose	3.33 Gm.
Distilled water, to make	100.00 cc.

Calculations made by the osmotic factor method (3) gave the results shown in Table II.

Comparing the osmotic factor of the nasal spray of 0.0594 with the osmotic factor of 0.0290 for an 0.85% solution of sodium chloride or 0.0308 for a 0.9% solution of sodium chloride, it is seen that the nasal spray is grossly hypertonic if judged by the osmotic factor method alone.

The freezing point of the nasal spray was found to be −1.17° C. By comparison with the freezing point of average blood, *i. e.*, −0.56° C., it is apparent that the freezing-point depression of the nasal spray is approximately twice as great as for average blood. Hence the nasal spray would be pronounced grossly hypertonic on the basis of the freezing-point method.

Wokes (4) has stated that, in general, if a solution when diluted with not more than half its volume of distilled water causes hemolysis of normal blood, the original solution probably is not isotonic with

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the blood and is scarcely suitable for injection. In order to apply this criterion, the nasal spray under consideration here was diluted with one-half its volume of distilled water and tested by the hemolytic method. The results showed definite hemolysis, indicating that the solution would be classed as hypotonic on the basis of the hemolytic method.

TABLE I.—FREEZING POINTS OF SOLUTIONS

Solution	Freezing Point, ° C.
Dextrose (monohydrated) 5% *w/v*	−0.53
Sodium chloride 0.85% *w/v*	−0.53
Isotonic Solution of Dextrose and Sodium Chloride N. F. VI	−0.54

TABLE II.—OSMOTIC FACTORS CALCULATED FOR NASAL SPRAY

Ingredient	Osmotic Factor
Ephedrine hydrochloride	0.0099
Menthol	0.0006
Chlorobutanol	0.0028
Alcohol	0.0293
Dextrose	0.0168
Total	0.0594

These results demonstrate the occasional unreliability of methods which are commonly used to adjust the tonicity of a solution. Here we have a nasal spray which is grossly hypertonic as judged by the osmotic factor method and freezing-point method, but is found to be hypotonic when tested by the hemolytic method. These differences show that sufficient consideration has not previously been given to the fact that the osmotic pressure and freezing point of a solution depend on the concentration of dissolved particles, while the tonicity of a solution depends on the concentration of dissolved particles which are unable to pass through the particular membrane which is being considered.

In the case of the nasal spray, it is quite evident that alcohol exerts its full effect in lowering the freezing point of the solution. Table II shows that the alcohol present in the nasal spray is practically sufficient to lower the freezing point to that of average blood, without any of the other ingredients of the formula. The question then arises as to whether alcohol acts like sodium chloride or other solutes in preventing hemolysis or whether it passes through the membrane of the corpuscles as water does. Before describing experiments on the permeability of red corpuscles to alcohol, some further experiments on the nasal spray will be outlined.

Tests were made on the nasal spray with modifications in the ingredients. Considering the osmotic factors in Table II, the total osmotic factor for the ephedrine hydrochloride, menthol and chlorobutanol is 0.0133. The osmotic factor of blood, taken as equivalent to 0.9% sodium chloride solution, is 0.0308. Subtracting the total osmotic factor of three ingredients mentioned from the osmotic factor of blood gives a result of 0.0175 for the osmotic factor of adjusting substance needed to make the nasal spray isotonic. Omitting the alcohol entirely and using dextrose as the adjusting substance, the usual form of calculation (3) shows that 3.466 Gm. of dextrose per 100 cc. of the nasal spray is required to make the solution isotonic with blood. Such a solution was prepared and found to have a freezing point of −0.62° C., indicating that the calculation by the osmotic factor method gave a solution which was slightly hypertonic as judged by the freezing-point method.

In another experiment the quantity of dextrose to be added was determined by the freezing-point method. A solution was made containing ephedrine hydrochloride, menthol and chlorobutanol, as listed in the formula for the nasal spray, but omitting the alcohol and dextrose. It was found that this solution had a freezing point of −0.25° C. Knowing that a 1% solution of dextrose causes a freezing-point depression of 0.10° C., and making the calculation in the usual way (3), it was found that 3.1 Gm. of dextrose per 100 cc. of nasal spray is required to make the solution isotonic with the blood, as determined entirely by freezing-point methods. A nasal spray was prepared omitting the alcohol of the formula and using 3.1 Gm. of dextrose per 100 cc. of spray. The freezing point of this solution was found to be −0.58° C. Thus a solution having a slightly greater freezing-point depression than desired was obtained when the calculations were made by either the osmotic factor method or the freezing-point method.

Effect of Various Substances on Hemolysis of Red Blood Corpuscles.—Experiments were carried out to determine the hemolytic effect of a number of substances, *i. e.*, ethyl alcohol, glycerin, boric acid urea, ammonium chloride, propylene glycol, diethylene glycol and carbitol. Alcohol and glycerin are frequently used in nasal preparations, and boric acid is commonly employed in collyria. Experiments on urea and ammonium chloride were carried out principally because of statements in the literature to the effect that these substances cause hemolysis of red corpuscles. Experiments on propylene glycol, diethylene glycol and carbitol were conducted as a matter of scientific interest and no recommendation is made for their possible use in parenteral solutions as no further physiological or toxicity tests were conducted.

The substances were first tested in concentrations equivalent to a 0.9% solution of sodium chloride in order to determine whether or not each substance prevents hemolysis when used in solution alone. Since a 0.5% solution of sodium chloride prevents hemolysis under the conditions of the test, each substance was added to 0.2% and 0.3% solutions of sodium chloride to make solutions of the same molar concentration as 0.5% sodium chloride solution. The results of these tests indicate whether the substance tested was able to prevent hemolysis when part of the osmotic pressure was supplied by sodium chloride. Each substance was also added to a 0.5% sodium chloride solution in quantity sufficient to make the total concentration of solutes equivalent in molar concentration to a 0.9% solution of sodium chloride. The latter tests were conducted because it was recognized that there was a possibility that some substances might cause hemolysis, even though the solution had an osmotic pressure which would ordinarily be sufficient to prevent hemolysis. In such instances, hemolysis might be due to some injurious effect of the substance on the corpuscular membrane. Each result was verified by repeated tests.

Before testing the various substances, experiments were conducted with sodium chloride and dextrose in order to have a definite basis of comparison. Sodium chloride prevented hemolysis when used in concentrations ranging from 0.45% to 0.9%; lower concentrations caused hemolysis. Tests with dextrose showed that 1% and 2% solutions caused hemolysis, a 3% solution gave partial hemolysis and in 4% and 5% solutions there was no hemolysis. The results with various other substances are shown in Table III.

Hemolytic tests were also conducted with solutions containing 1% of various substances and 0.9% sodium chloride. In such tests carbitol caused hemolysis but there was no hemolysis with alcohol, glycerin, propylene glycol or diethylene glycol. The results were the same when the percentage of substance was 5% instead of 1%.

Hemolytic tests on 1, 2, 3, 4 and 5% solutions of boric acid resulted in hemolysis in each case. These results showing that boric acid does not prevent hemolysis are in agreement with the report of Wokes (4).

equivalent to 0.5 or 0.9 per cent sodium chloride prevent hemolysis in every case.

Urea does not prevent hemolysis when used in a concentration equivalent to 0.9 per cent sodium chloride. Urea has some effect in preventing hemolysis when used in presence of 0.3 to 0.4 per cent of sodium chloride, which by itself would not prevent hemolysis in these concentrations. Ebina (5) reported that urea in concentrations of

TABLE III.—THE EFFECT OF VARIOUS SUBSTANCES ON HEMOLYSIS[a]

Concentration			Results of Hemolytic Tests								
Conc. of NaCl, %	Conc. of Substance in NaCl Equiv., %	Total Conc. in NaCl Equiv., %	Dextrose	Urea	Ammonium Chloride	Boric Acid	Ethyl Alcohol	Propylene Glycol	Glycerin	Diethylene Glycol	Carbitol
0	0.9	0.9	—	H	H	H	H	H	H	H	H
0.2	0.3	0.5	—	H	H	H	H	H	H	H	H
0.3	0.2	0.5	—	—	H	H	—	—	—	—	H
0.4	0.1	0.5	—	—	—	—	—	—	—	—	—
0.5	0.4	0.9	—	—	H	H	—	—	—	—	H

[a] Abbreviations used: H = hemolysis; — = no hemolysis; conc. = concentration; equiv. = equivalent molar concentration.

DISCUSSION OF RESULTS

Freezing-Point Apparatus.—Tests made with the Bartley and Beckmann freezing-point apparatus showed that the two methods gave comparable results. The Bartley apparatus was easier to operate and the tests could be completed in about one-third the time required by the Beckmann method.

Hemolytic Method.—The hemolytic method is less convenient to carry out than the freezing-point method. The freezing point of a solution can be determined very accurately, but when the freezing-point data are applied in preparing isotonic solutions, the results may be very erroneous. The reason for the possible error is that the freezing-point method measures all dissolved particles (molecules or ions), while isotonocity depends on having an equal concentration of particles which are not able to pass through a particular membrane. As an example from the previous literature, red blood corpuscles are said to be permeable to urea and ammonium chloride. From such statements one would conclude that these substances lower the freezing point of water but are of no avail in preventing hemolysis. Hence in using freezing-point data, it is important to make hemolytic tests to establish whether or not the results are applicable to parenteral solutions.

Effect of Various Substances.—The results in Table III show that the nine substances tested fall into three different groups as far as hemolytic effect is concerned. Dextrose and sodium chloride in various proportions 0.5 to 6 per cent caused hemolysis independently of the concentration of sodium chloride.

Ammonium chloride and boric acid gave similar results in that neither substance prevented hemolysis in any of the concentrations used, except when the concentration of sodium chloride was almost sufficient to prevent hemolysis and the concentration of ammonium chloride or boric acid was low. In a molar concentration equivalent to 0.4 per cent sodium chloride, both substances caused hemolysis even in the presence of 0.5 per cent sodium chloride, which ordinarily is sufficient to prevent hemolysis. Osmotic pressure considerations alone appear insufficient to explain these results; apparently boric acid and ammonium chloride bring about the release of hemoglobin by some other mechanism, perhaps by dissolving some constituents of the membrane and thus changing its permeability. Another explanation was given for ammonium chloride by Jacobs (6) who stated that ammonium salts produce hemolysis even when solutions are isotonic with the interior of the cell because these salts furnish ammonia, which is a readily penetrating substance.

Alcohol, glycerin, propylene glycol and diethylene glycol gave identical results. In concentrations having the same osmotic pressure as the blood, these hydroxy compounds fail to prevent hemolysis. Hemolysis is prevented in presence of 0.3 per cent or more of sodium chloride, with sufficient of the hydroxy compound to bring the total molar concentration up to the equivalent of a 0.5 per cent solution of sodium chloride.

Carbitol fails to prevent hemolysis except when the concentration of sodium chloride is almost sufficient to prevent hemolysis and the carbitol concentration is only 0.1 per cent. Higher concentrations of carbitol induce hemolysis even in presence of sufficient sodium chloride ordinarily to prevent hemolysis. In this respect, carbitol behaves similarly to ammonium chloride and boric acid.

It has been known for almost half a century that certain substances penetrate erythrocytes. Thus in 1896 Gryns (7) showed by chemical methods that erythrocytes of chicken blood were permeable to urea. Using the hemolytic method, he found that erythrocytes were permeable to alcohol and glycerin but not to dextrose or disaccharides. Hedin (8) in 1897 showed that the red corpuscles of ox blood were permeable to urea, glycerin and ethylene glycol but not to dextrose or sucrose. Similar studies have been made by a number of later investigators (9). In the past, these results have failed to receive proper attention in relation to their application in the preparation of pharmaceutical isotonic solutions.

There is considerable difference in the permeability of red corpuscles of different species of animals (10). Hence much of the past work does not apply to human blood. For definite results of pharmaceutical value, the importance of using human blood, as was done in the present investigation, is apparent.

The most commonly accepted theory of hypotonic hemolysis is that red corpuscles placed in a solution of lower osmotic pressure take up water which finally causes overdistention of the corpuscles and rupture of the corpuscular membrane, thus releasing the hemoglobin. There is also a theory that hemolysis is brought about when protoplasmic colloids swell sufficiently to liberate the hemoglobin. The results of the present investigation could be stated in terms of the latter theory by a simple change in terminology.

SUMMARY

Research was conducted on the technique and applicability of freezing-point methods, and the results were correlated with calculations by the osmotic factor method and with the results of hemolytic tests.

Freezing-point determinations can be carried out more easily and more quickly by the Bartley method than by the Beckmann procedure.

Tests on a nasal spray show that freezing-point data and osmotic factor calculations may give unreliable results in the preparation of isotonic solutions. It is recommended that the results be checked by the hemolytic method.

Employing human blood in the hemolytic method, it was found that urea, ammonium chloride, boric acid, ethyl alcohol, glycerin, propylene glycol, diethylene glycol and carbitol failed to prevent hemolysis when used alone in aqueous solutions of a concentration isosmotic with the blood. These substances are able to contribute slightly to the prevention of hemolysis, if used in low concentrations in presence of appreciable concentrations of sodium chloride.

Ammonium chloride, boric acid and carbitol, in moderate concentrations, appear to liberate hemoglobin by some mechanism other than osmotic effects, perhaps by changing the permeability of the corpuscular membrane.

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Nomenclature of Peppermint and Its Varieties*,†

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Peppermint is cultivated on a larger scale than any other herb used in medicine or in the pharmaceutical, aromatic and cosmetic industries (1).[1] The average annual production of the volatile oil of peppermint during the period 1930–1939, inclusive, in the United States alone was 851,000 pounds, obtained from an average planted area of 35,049 acres. In 1935, 1,352,000 pounds of oil were produced (2).

The states now chiefly active in peppermint oil production are Indiana (northern), Michigan (southwestern), Washington and Oregon (western parts), and Ohio (northwestern). In the past, peppermint oil has also come from New York,[2] western Massachusetts[3] (3, 4), Illinois, North Carolina (eastern) (5), California (northern), Iowa (6), New Jersey (western?) (7) and Wisconsin (8).

Peppermint herb is marketed in some of the states mentioned, notably North Carolina, and was said in 1929 to be produced in relatively small amounts also in Arkansas, New York and Idaho (9). Most of the American herb has been and is obtained from wild-growing plants (10).

Peppermint, either as leaf or herb, is or recently was, official in twenty-one of the important national pharmacopœias of the world (11). It appears to be lacking only in the British, Finnish and Japanese[4] pharmacopœias. Oil of Peppermint (true) seems now to be official in all current pharmacopœias except the Japanese.

Despite its extensive production and usage, much difference of opinion prevails as to the names, both scientific and vernacular, which should properly be applied to the species and its subdivisions. The terminology is reviewed and an effort made at evaluation in the present paper.

NOMENCLATURE

The botanical name universally recognized for true peppermint is *Mentha piperita*. There has been some disagreement over the spelling of this binomial. Thus, *Menta* is preferred by some botanists (12, 13), because this was the spelling used by Ovid, Pliny, Columella and other Latin writers. Logically, however, the spelling "Mentha" should be preferred since it represents the latinization of the earlier Greek name "Minthe," this title most probably originating from the famous Greek legend of the nymph Minthe (Hippocrates).[5] However, it may possibly be derived from the old Hindu root "manth" or "mante" meaning "to rub," in reference to the use of the herb as a rubefacient[6] (14).

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[1] Recently peppermint has been classed by the U. S. Dept. of Agriculture as an essential war crop, and a recommendation to defer from military service those farmers engaged in the production of this and a few other essential drug plants has been made.

[2] A younger member of the Burnet (or Burnett) family who migrated to Phelps, New York, from the peppermint farming region at Ashfield, Mass., about 1816 started growing this crop with stock procured from the latter place. It soon developed into a large and prosperous industry, but was in its turn displaced by production in Michigan. Peppermint oil industry was discontinued in Wayne County, New York, about 1911.

[3] The first commercial peppermint cultivations in this country of which we have record occurred in Ashfield, Mass., about 1812, when Samuel Ranney came there from Chatham, Conn. He started distilling and his neighbors imitated him, until by 1821 there were five and by 1830 ten distilleries in the vicinity of Ashfield. Soon the oils and some simple preparations were being widely peddled throughout the United States. The population of the town was increased considerably and by 1825 several hundred acres of peppermint were in cultivation; the value of the oil production here in 1824 was estimated to be over $40,000. With the development of the New York peppermint industry, however, most of the peppermint producers migrated thither, and the Massachusetts industry suffered a permanent decline. (Howes, Frederick G., "History of the Town of Ashfield, Franklin County, Mass., from its settlement in 1740 to 1910 . . . Ashfield," *ca.* 1912, p. 103, 126.)

[4] *Pharmacopœia Japonica IV* (1922) (p. 180) recognizes under *Folia Menthae* the leaves of *M. arvensis* L. var. *vulgaris* Bentham (Japanese mint).

[5] *Mintha* and *Minthe* have also been proposed (16) as generic names, the latter being considered preferable because used more frequently by the Greeks (*μίνθα*, Pliny, Theophrastus; *μίνθη*, Hippocrates; *cf.* *μινθος*).

[6] Aside entirely from its etymological derivation, the spelling *Mentha* is, of course, permanently established by Linnaeus' usage (1753).

Flueckiger (15) has pointed out that *piperita* is really a corruption of the earlier used, more correct designation *piperata* or *piperitis* first employed in England. The species name *piperata* was used by Petiver (17), John Hill (18), Stokes (19), S. F. Gray (20), Tschirch (21) and others.

In earlier editions (22) of the London Pharmacopœia, "Mentha piperitis" appeared as the recognized name of the crude drug, this becoming "Menthae piperitidis folia" in later editions (23). The botanical names appearing alongside are respectively *Mentha . . . piperis* Ray[7] and *Mentha piperita* Linn.

English names which have been applied to *Mentha piperita* are: Peppermint[8] (formerly Peper-Mint (25) or Pepper Mint *e. g.*, (26)), Common Peppermint (27), Pepper Mentha (28), True Pepper-Mint (var. *officinalis*) (29), Peppery Mint (30), "Mint,"[9] Brandy Mint, Lamb's Mint (also Lamb Mint, Lammint), Eales' Peppermint (17), Essex Peppermint (17), Garden Peppermint, etc.

Flueckiger (31) denoted as Peppermint any *Mentha* species possessing to a high degree the ability to produce menthol. Several members of the genus are known to contain menthol in substantial proportions and hence are called peppermints. However, the term with or without qualifying noun or adjective has also been applied to species which contain very little or no menthol and even to other genera (such as *Thymus, Eucalyptus*, etc.). Therefore in view of the rather indefinite application of the term as now used, it would seem best to ignore Flueckiger's proposal and restrict the use of "Peppermint" to *M. piperita* and varieties. The rather distantly related species *M. canadensis* L. var. *piperascens* Briq. thus might better be spoken of as Japanese Mint than as Japanese Peppermint, as now generally known, *M. canadensis* L. var. *glabrata* A. Gray as Chinese Mint rather than Chinese Peppermint, and *M. arvensis* L. var. *javanica* Hook. as Javanese Mint rather than as Javanese Peppermint. There would thus be avoided some of the considerable confusion to which these four species, and others to a lesser extent, are subjected so frequently.

The genus *Mentha* and its individual species are the objects of considerable controversy in classification and genetics. In addition to the subspecific groups which have been recognized by some botanists, there are a number of horticultural forms that are mentioned or described in the literature at various times but which appear to have achieved no general scientific recognition.

Because type specimens of most species of *Mentha* are to be found only in certain European herbaria, it is not possible to carry on critical taxonomic studies of the genus in this country at present. It is therefore necessary to consider and evaluate the opinions of reliable workers who have published their findings in past years. It is requisite to keep in mind the recognized fact that many students have named "species" of *Mentha* which are illusory or at best most difficult to define (34). Thus, Gandoger (35) named about 270 "species" (?),[10] none of which apparently is now recognized under the name he used. Others who added to the confusion were Sole, Opiz, Host, Lejeune, Smith, Boreau, Timbal-Lagrave, Strail, Kerner, Déséglise and Durand, Weihe, Moench, Beck von Mannagetta, Nees, Jacquin, *et al.*

Workers like A. Pérard, Malinvaud, Briquet and others are considered more judicious in their classification of species, and it is therefore to such workers we should turn for a more lucid interpretation of this difficult group. The effort is here made briefly to compile and compare taxonomic views having pharmacognostic import.

The name and definition of *Mentha piperita* are frequently based on the authority of the description and herbarium specimens of Linnaeus. Among those accepting Linnaeus' naming have been A. Gray (36), Wirtgen (37), Braun (38), Sagorski and Osswald (39), Britton and Brown (40) and others. Most of the important pharmacopœias of the world, including the latest editions of the U. S., British, Swiss, Belgian, French and Brazilian pharmacopœias, employ the Linnaean name.

Some workers, however, have preferred to recognize the descriptions of other authorities, and for stated reasons. Thus, Briquet, generally conceded the outstanding student of *Mentha*, has preferred to base this species on Hudson (41, 125), later (42, 43, 106, 134) accepting the Linnaean concept in part (*M. piperita* (L. *ex parte*) Hudson). He accepted (41) the views of Smith (33, 44) and Baker (45) that the *M. piperita* of Linnaeus was actually only a pubescent form of *M. hirsuta* L. Mant. 81 (according to Smith, var. γ), or what is now known as *M. aquatica* L. (*M. aquatica* L. subsp. *Bakeri* Briq.). Briquet states (42): "*descriptione cum planta non male quadrante et syn. Rayi recto non herb.!*" (description matching not badly with the plant and correctly for the synonym(s) of Ray but not for herbarium specimen!).

Others, however, have objected also to the description of Linnaeus (Spec. Pl., 1753). This may be due to the description of the leaf as lanceolate (it is more typically ovate) or, more likely, to reference to it as subpetiolate[11] (it is distinctly petiolate). This description is emended in the second edition (Spec. Pl., 1763) to read "*. . . foliis ovatis . . . petiolatis.*"[12]

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[7] *Cf.* Mentha piperis sapore. Blackwell Hb. (24).

[8] This and the Latin *piperita* (*piperata*) originate, of course, from the "much stronger and warmer taste [than of the other mints], pungent and glowing like pepper, and sinking as it were into the tongue" (32). Remarkable persistence of pungency has been noted, thus by Stokes (19) in specimens over fifty years old, by Smith (33) in a specimen eighty-five years old or older.

[9] "Mint" refers in the botanical sense to any member of genus *Mentha*, but is occasionally used to refer to the family *Labiatae* (Mint family) or to any of its members. In the vernacular vocabulary of most regions, "mint" when used in the specific sense refers to Spearmint. However, in the words of the Bureau of Chemistry, U. S. Department of Agriculture: "When such products as confectionery or chewing gum are labelled with such terms as 'peppermint,' 'mint,' or 'mint flavored,' there is no question that the purchaser expects to obtain a product flavored with genuine peppermint oil." (*Perfumery Essent. Oil Record*, 16 (1925), 111).

[10] Gandoger's binomials are now generally regarded as representing some undefined subspecific group.

[11] Thomas Martyn (51) in 1793 defined "subpetiolatus" as " . . . scarcely petioled, or with a very short petiole." A. A. Crozier (52) gives the meaning of "subpetiolate" as " . . . having a very short petiole; subsessile."

[12] Berg and Schmidt (24) feel that Linnaeus' diagnosis applies to *M. piperita* as we know it and that therefore it is immaterial what specimens occur under that name in his herbarium. However, Baker (45) claims the real peppermint " . . . was misunderstood by Linnaeus, as both his herbarium and descriptions testify."

J. E. Smith (33) in 1799 accepted Hudson's description for peppermint and rejected Linnaeus' authority, inasmuch as he had found the latter's herbarium specimen[13] not at all the true English peppermint but one " . . . quite distinct from ours, from which it may at once be known by its very hairy flower-stalks and calyx. It is merely a variety of the *M. hirsuta* of Linnaeus with the flavour of pepper-mint . . . " Later he says ". . . the *Mentha piperita* used in Sweden and described by Linnaeus and Bergius,[14] is certainly a different species from ours . . . . " Under *M. hirsuta* Linn. Mant. 81, he states: "This is the *M. piperita* of Linnaeus and Bergius, cultivated in the north of Europe for Pepper-mint. Linnaeus' specimen is from the Upsal garden, and has the flavour of our *M. piperita* very strong. This circumstance led him to consider it as the plant of Ray and Dillenius."

Because Smith was the first to define *M. piperita* clearly and completely enough, he has been cited by several workers, including Bentham (26), Planchon and Collin (48), Lindley (46), Bentley and Trimen (65) and Peckolt (49).

Others again have felt Hudson's treatment (50) adequate.[15] Some of these are: de Candolle and Lamarck (53), Woodville (64), Timbal-Lagrave (54), Flueckiger and Hanbury (55), Malinvaud (56, 57), Sowerby (58) and Topitz (59).[16]

Still other workers either have not troubled to settle for themselves the involved controversy over the name or else have felt perhaps that it would be difficult now to determine which author should correctly receive credit. Thus, Rouy (66) denominates the species as "X *M. piperita* Huds. (*pro sp.*); L *p. p.*; Briq. *et auct. mult.*" A. and E. G. Camus (61) refer to "X *M. piperita* L., Huds., Schultz, Malvd., Briquet, *et auct. mult.*"

To avoid useless argument, the species has sometimes been cited simply as *M. piperita au(c)torum* (abbr. *auct.* or *aut.*), a practice still occasionally seen (67). In accordance with the present International Rules (143), it would seem proper to modify Linnaeus' authorship only so far as to amend it, thus rendering the name as *M. piperita* L. *pro parte*, Hudson; this would seem to have precedence over Briquet's rendering as "*M. piperita* (L. *ex parte*) Hudson" (43).

Beginning with Schultz (60), many writers have recognized *M. piperita* as a hybrid species. Malinvaud developed the species vigorously from this viewpoint and was sustained by Briquet, Gillot, Focke, Tschirch (43), Camus (61) and others. Where the hybrid origin of this species is recognized, the scientific name has been rendered (62): X *M. piperita* (Huds.) Rouy (*M. viridis* X *aquatica*). It should be borne in mind that some botanists (*e. g.*, Linnaeus, Hudson (50), Wirtgen (37), Schumann (63), *et al.*) have regarded *M. piperita* as a true species, not a hybrid, and that among those holding to the hybrid view there is difference of opinion as to ancestral identities.

As would be expected, there are numerous taxonomic synonyms and some homonyms for *Mentha piperita*. Lists of these have appeared in Smith (33), Hayne (68), Stokes (19), Bentham (26), Berg and Schmidt (24, 63), Britton and Brown (40) and elsewhere.

IDENTIFICATION

Errors are frequently made in the identification of *Mentha* species. The particular importance of proper determination of plant materials used for phytochemical study is well illustrated in the case of some supposedly abnormal peppermint oils studied at the University of Florida. In this work (69), a serious effort was made to identify the plant stock from standard botanical descriptions, then later to confirm identification by sending specimens to the Division of the Bureau of Plant Industry (Washington, D. C.) whence the plant had been obtained. It was concluded that the clon represented *M. piperita*. Approximately ten years later, further more detailed studies were made of these same oils which had been put away. In this work (70), it was assumed that these oils had originated from true peppermint.

Subsequent examination by the writers of an herbarium specimen[17] labeled as representing the peppermint of the Thesis (69) and of properly identified photographs of specimens of the same stock revealed that the plant in question was a member of the section *Verticillatae* Linn. (*Arvenses* Benth. (71)) and not of section *Spicatae* Linn.[18] to which true peppermint belongs. Tentative identification was made as probably *M. canadensis* L. (*M. arvensis* L. var. *canadensis* (L.) Briquet).[19]

Although no further evidence is required, the following substantiating facts are of interest:

1. One peppermint clon obtained from Oregon and studied at the same time produced an oil having a good menthol content. Why did this clon not "degenerate" as the Bureau of Plant Industry stock presumably did? Likewise over a period of years there were no indications of decreased menthol content in Japanese mint plants growing in adjacent plots (72).[20]

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[13] Smith had purchased the Linnaean herbarium and thus had first-hand knowledge of the specimens of which he speaks.

[14] Bergius' (120) more detailed description of *M. piperita* L. merits study: he noted the stem as hairy, leaves short petiolate, ovate-oblong, pubescent on both sides, and calyx as hairy. This conflicts with the usual description of stem smooth or nearly so, leaves all petiolate, ovate, generally smooth, and calyx entirely smooth at the base (33).

[15] Smith referred *M. piperita* Hudson to his own variety of the same species, *α foliis ovato-lanceolatis*.

[16] Pharmacopœia Argentina (III, 1928) recognizes Hudson's authorship.

[17] Now deposited in the Herbarium of the School of Pharmacy, University of Florida. It is unfortunate that when phytochemical studies are made, it is not everywhere a routine procedure for possible future reference to deposit herbarium specimens of the plant material being investigated.

[18] Peppermint is sometimes regarded as a hybrid of species from sections *Spicatae* Linn. and *Capitatae* Linn.

[19] Epling (74) on the basis of photographs suggests that these plants can most assuredly be classified as belonging to the *M. arvensis* complex (which includes *M. canadensis* as one species); beyond this stage of determination it is difficult to go (he says) since the differentiation of species within this complex is based to a considerable degree on geographical origin.

[20] Sievers and Lowman (75, 76) have shown that there is no noticeable decrease in menthol content of Japanese mint oil for plants cultivated in one area over a period of years.

2. Reference in the Thesis and on the oil bottle labels relates variously to "American Peppermint" and "American Mint." Since "American Mint" is a common name for *M. canadensis*, this points to the possibility that someone in the repeated processes of stock planting and handling may have relabeled as "American Peppermint" what originally had been properly tagged as "American Mint" or possibly "American Wild Mint."

3. The governmental division which had supplied the stock to Florida was not altogether positive regarding identity of this material (73).

4. Constants for the oil of the supposed peppermint are similar to those for oil of *M. canadensis*, whereas mostly widely different from constants for the usual peppermint oil. (See Table I.)

It is of interest to note here a number of "abnormal" oils studied several years ago at the University of Wisconsin. Some Japanese peppermint oils (stock from the Bureau of Plant Industry, Washington, D. C.) were found to consist largely of pulegone and *l*-limonene and to contain no menthol or menthone (77, 78, 79, 80, 81, 82). The reported composition corresponds quite closely with that of oil of *M. canadensis* L., as determined by one of these workers (83). In another study, (84, 80), there were indications of the presence of pulegone in reputed *M. piperita* L. (*cf.* 85, 86).[21] Data for some of these oils are tabulated for comparison in Table I.

A study of Table I will suggest that errors in identification of plant materials would possibly account for reported abnormalities in at least some of these mint oils.[22]

VARIETIES OF PEPPERMINT

It is essential in such various fields as horticulture, phytochemistry and genetics to give close attention to plant classification not only in the determination of species but also of subspecies and of smaller di-

TABLE I.—CONSTITUENTS AND CONSTANTS OF VOLATILE OILS OF VARIOUS *Mentha* SPECIES

Constant or Constituent	True Peppermint, U. S. P. XII or Standard Analyses	So-called Peppermint, Univ. Florida, 103a 1932–1933 (69)	So-called Peppermint, Univ. Florida, 103a 1940–1941 (70, #2, 93)	*M. canadensis* L. (83)	*M. arvensis* L. (145)	"Japanese Mint," 1922 (96)
Specific gravity (25° C.)	0.896–0.908 (U. S. P.)	0.9213	0.9275 25°/25°	0.927–0.935/20° 0.931 (142)	0.9351/15°	0.924
Optical rotation, $[\alpha]_D$	−18° to −32°/25° (U. S. P.)	+16.893°	+13.65°/20°	+16° 11′ to +20° 32′ (142)	+14.32°	+15.4°/21°
Refractive index, n_D	1.4590–1.4650/20° (U. S. P.)	1.48057	1.48057/20°	1.4835/25°	1.4846	1.484/22°
Saponification value	27.1 (95)	11.85	...	0 to 5.6	...	...
Acid value	0.00 (92)	0.79	2.33	5.6 (cohobated)	...	...
Ester value	29.72 (92)	11.069	13.10	11.2	33.6	...
Same after acetylation	154.7 (92)	30.01	36.49	33.6	134.1	...
Total alcohols, %	Not less than 50 (U. S. P.)	7.23 (94)[b]	(12.43)[a]	9.6 (not menthol)	No menthol detectable	17.3 No menthol found
(Total menthol, %)	Up to 68 (135)	11.62[b]	...	15.96 (138)		
Free alcohols, % (Free menthol, %)	(Not less than 46.1)[a] (U. S. P.)	8.55 ...	8.55 9.01	6.5 7.9 (138)	... ...	12.1
Combined alcohols, % (Ester menthol, %)	(Not less than 3.9)[a] (U. S. P.)	3.07 ...	(3.65)[a] ...	(3.1)[a] 8.06 (138)	... ...	(5.2)[a] ...
Menthyl ester as acetate, %	Not less than 5 (U. S. P.)	3.013	4.63	4.0	...	6.6
d-Pulegone, %	None or up to 2% (?) (92)	*ca.* 80. (94)	87 (as ketones)	90–95	Present	86
Menthone, %	8–20–23 (138)[c]	...	...	...	13–17	None reported
Other ketones	"Menthenone" (138)	...	*d*-Iso-menthone. *l*-Methylcyclohexanone-3	Piperitone. *l*-Methylcyclohexanone-3, perhaps (138)	Piperitone	...
Other compounds	*l*-Limonene (95)	...	...	*l*-Limonene	...	*l*-Limonene

[a] Figures in parentheses are estimated from other figures given.
[b] Although calculated as menthol, apparently only a fractional part represented this alcohol. Bureau of Plant Industry figures for the same oil were slightly higher.
[c] Sometimes menthone content considerably larger, thus to 42% (144).

[21] Herbarium specimens of the various mints used in this work could not be obtained for study from the University of Wisconsin.

[22] Other examples of misidentification of mints are not lacking. A recent medical writer (87) described cases of dermatitis caused by "horse mint," which had been identified as *M. citrata*. On examination, this proved not to be that at all but to be probably *M. sylvestris*. In the same paper, reference is made to *M. vera*, a name having no botanical or pharmacognostic significance. Allard (88) conducted experiments on photoperiodic behavior in a series of mints. Among these, what he describes as *M. piperita* var. (obtained from Greensboro, N. C.) appears actually to have been Japanese Mint, both because of the particular reaction to varying day-lengths (earlier blooming than true peppermint) and from the appearance of the plant in the photograph. Frequent reference is made in the literature to peppermint seed (germination, propagation of stock, etc.). It has, of course, been thoroughly shown that viable seed of peppermint is practically unknown, it is so rare. Errors of nomenclature in the literature are much too frequent. As one instance from many, Black and White Peppermints are occasionally named as *M. piperita* var. *nigra* and *alba* (resp.) or as *M. piperita rubescens* and *pallescens* (resp.).

visions. Many taxonomists do not concern themselves with determination farther than the species, but men who work with medicinal, aromatic, ornamental and other economic plants generally find it necessary to consider subdivisions of the species because of the great variability in chemical and physiological make-up often noted within a single species.

A large number of subspecies, varieties and forms of *M. piperita* have been described. John Briquet's compilation in Tschirch's Handbuch (43) comprises 18 varieties divided among three subspecies. The older nomenclature for varieties authored by Sole (29) is still sometimes accepted (*e. g.* Bailey (98), Holmes (90, 91) . This will be alluded to later.

The recent use of simplified terminology, such as "*Mentha piperta* L. var. Mitcham" used by Swanson and Nelson (150), would appear justified in view of the present disposition of students to simplify the nomenclature of subspecific forms when these are numerous (100). Stout (151) proposed the form *Mentha piperita* L. clon(e) Mitcham. More recently, indeed, he (152) recommends the name of a clon to be simplified even further—thus, in the present case, to *Mentha*, Mitcham or Mitcham Peppermint. The version *M. piperita* L. Mitcham is perhaps more acceptable to some. Besides simplification, the most distinct advantage of such nomenclature is that it identifies the subject as a clon.

Many forms of peppermint have been described, a considerable proportion of which are thought of little or no significance. Here will be discussed only those generally acknowledged as of definite economic importance.

The three forms of peppermint prominent in the United States and in parts of the British Empire (among other places) are "Black Mitcham," "White Mitcham" and "American." Sole's (29) classification of *piperita* into var. *officinalis*, *vulgaris* and *sylvestris* was followed by the careful modern studies of A. and E. G. Camus (61), Briquet (42), and others. In the descriptions following, preference is given to the nomenclature of the later writers, with the older names presented underneath as possible synonyms.

1. *Mentha piperita* L. *pro parte*, Huds. subsp. *piperita* Briq. var. *officinalis* Briq. forma *rubescens* Camus (61).
   Black Peppermint; Black Mint; English (or Mitcham) (Pepper)mint; Black Mitcham; (English) "Black Stem"; Mitcham Red; "Purplestem"; Rote Minze (Red Mint); "Wild Pepper-mint" (58); etc.
   Syn.: *M. piperita* L. var. *vulgaris* Sole (97, 98, 99, 100, 136).
   M. piperita var. β Smith.

This is the only form of peppermint which at present is cultivated to any extent in this country and it is also probably the commonest cultural form abroad. It was introduced into Michigan from England in 1892, and soon proved to be a thriftier and hardier plant than the American peppermint which had been grown in Michigan almost exclusively up to that time. Tschirch (43) on careful examination of herbarium specimens could find no notable differences in the English and American Black Mitcham plants, so concluded them identical.[23, 24]

2. *M. piperita* L. *pro parte*, Huds. subsp. *piperita* var. *officinalis* Sole forma *pallescens* Camus (61).
   White Peppermint; White Mint; Mitcham (Pepper)mint; White Mitcham; "White Stem"; Mitcham White; Gruene Minze (Green Mint); Garden Pepper-mint; etc.
   Syn.: *M. piperita* L. var. *officinalis* Sole (97, 98, 99, 100, 136).
   M. piperita var. α Smith.
   M. Hudsoniana Braun.

This plant does not seem to be cultivated now commercially in the United States, but is still grown somewhat in the old country, notably in England, and formerly was cultivated in western Michigan, Indiana, etc. (105).

Bentley and Trimen (65) pointed out that the black and white forms possess essentially the same botanical characters, but differ in habit sufficiently to make a distinction possible, this chiefly based on stem color (as the common names indicate).

3. *M. piperita* Huds., form standing between var. *citriodora* G. F. W. Meyer (var. *citrata* (Ehrh.) Briq.) and var. *calophylla* Briq. (43).
   American Peppermint; American Mint; State Mint (107); "Old Style" (Wayne County, N. Y.); "Western Mint" (?); "Michigan Mint" (?); New York State Mint; etc.
   Syn.: *M. piperita* L. (typical) (97, 98, 99, 100, 136).
   M. piperita L. var. *sylvestris* Sole (?) (see Table II).

This form is said to have been introduced into Wayne County, N. Y., from England and was probably the earliest form brought here.[25] Its common name may originate from the misconception that it was a native plant, also from its antedating Mitcham Mint.

American Peppermint is now quite generally excluded from cultivation. It sometimes occurs in Michigan fields, where insufficient care has been given to weeding it out in the fall prior to collecting

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[23] Most dependence for differentiation of these forms must be placed on the habit of the plant, an ensemble of characteristics which does not lend itself easily to study from the dried specimen or to verbal description.

[24] However, Holmes (102) thought the French forms of Camus do not correspond to the black and white English forms (also opinion of Gattefossé (89)). The Camus forms are also thought (104) not to correspond with the "blanche" and "noire" forms of Planchon and Collin (48).

[25] Peppermint is mentioned (137) in 1806 as an American garden plant. It was first distilled here in quantity in 1816 (43).

the runners for propagative purposes.[38] In the field, it is quite readily recognizable to the trained eye and is easily "rogued out" (107). American mint was reported in 1904 as no longer grown in New York State because of poor oil productiveness (109). In 1922, English peppermint was reported (110) grown in pure stands throughout Michigan, except around Charlotte, where some admixture with American was noted. The "Western" or "Michigan" oils of two generations ago and earlier (oils with relatively lower total and ester menthol content) represented American peppermint oil apparently, whereas the superior "New York State" oil (with relatively higher total and ester menthol content) came from Mitcham plants.

Inasmuch as living plant material of the various forms of peppermint was not available, only a literature survey could be made at this time of distinctive characteristics (Table II).

In Europe, other cultural types of peppermint have been discussed. Thus, Italo-Mitcham Mint is Mitcham (either white (43, 111) or black (112, 113)), which has become acclimated in Italy after growing there for a few years, or in some cases since 1865–1879. Franco-Mitcham Mint applies to Mitcham Peppermint (especially white) which has been grown a few years in France, sufficient to become acclimated. There are other types of hyphenated Mitchams, such as that of Romania (Roumano-Mitcham).

Flueckiger (31) indicated that peppermint forms cultivated in England, Germany, France and North America vary from one another. Umney (114) considered that different black (or red) and white varieties were grown in France, Italy and Sicily.

Timbal-Lagrave claimed (54) that the "peppermint" cultivated around Toulouse (*ca.* 1860) was identical with a form described by Wirtgen (139) as *M. piperita α Langii* Koch: this is now generally interpreted as *M. suavis* Gussone (140). White Mitcham is the mint chiefly grown in France (43).

In Germany, peppermint was made popular by Knigge (115). It is said (116) that three cultural forms are commonly raised: Mitcham, Palatinate and Thuringian. Palatinate peppermint is said (117) to be a cultural sort of var. *officinalis*, while Franconian (another less well-known peppermint) appears to be a different sort of the same variety (117). Thuringian peppermint is sometimes referred to also as a horticultural sort of var. *officinalis* (117), but Hegi (118) refers it to *M. dalmatica*

TABLE II.—DIFFERENTIATION OF BLACK MITCHAM, WHITE MITCHAM AND AMERICAN PEPPERMINTS[a]

	(*A*) Black Mitcham	(*B*) White Mitcham	(*C*) American Peppermint	*M. piperita* var. *sylvestris* Sole[b]
Habit	Much coarser plant than *B*	Smaller plant than *A*	Lower growing than *A*	Larger and coarser than *A*; wild appearance (29)
Stems	More or less splashed with purple; slightly hairy	Green	Green; slightly hairy	Hairy (29); reddish toward fall
Leaves	Dark olive-green, more or less splashed with purple	Lighter green than *A*	Lighter green than *A* (47)	....
	Less lanceolate than *B*, more ovate, broader ("broad-leaved p. m." (148)). Shorter, sub-elliptic. More rounded at base, short petioles. Finely serrate.	More lanceolate than *A*; ovate-lanceolate; rel. long and narrow ("narrow-leaved p. m." (148)); cuneately narrowed at base; distinctly petioled. Much more deeply and sharply serrate than *A*[c]	More ovate than *A* or *B* (101); rounded to cordate at base. Petioles and veins on lower side slightly hairy (101). Thinner texture than *A* (47)	Cordate-ovate or ovate; broader; slightly hairy on veins and petioles (29, 44)
Flowering	Stated infrequent in England, but this questioned. Flowers later than *B*	Often blooms in England when *A* does not. Flowers earlier; in Italy, *ca.* 20 days	....	....
Inflorescence	Lateral branches mostly in form of near globose "capitula" or short "spikes." Denser and more obtuse than of *B*	Oblong "spikes," more or less interrupted at base, longer on principal axis. Longer, looser and sharper than in *A*. Grayish, paler purple than *A*	....	Stouter (44). Paler color than *A*
Calyx	Glabrous at base; glabrescent at apex; teeth with rather fewer hairs than in *B*	Almost entirely glabrous; teeth with hairs more numerous toward apex than in *A*, shorter	....	....
Cultural requirements	Hardier than *B* and even than *C* after acclimation. Needs less care than *B* (fertilizer, water, etc.)	Less vigorous than *A* or *C*	Hardy and vigorous	Wild growing
Yields	Larger amount of herb and oil than *B* or *C*	Smaller than *A*	Much less volatile oil than *A* (47, 124)	....
Volatile oil quality	Lower than of *B* (121). More pungent, more total menthol, lower % ester, more menthone than in *B*	Higher priced than *A*, more delicate aroma (some disagree (122)). Greater opt. activity	Lower than *A* or *B*	Disagreeable odor

[a] On the basis of descriptions by various writers (29, 44, 61, 65, 114, 146, 147).
[b] The description of this variety (Savage Pepper-Mint) is included here because reminiscent of that for American Peppermint.
[c] Lamina has been described as in shape somewhat like that of spearmint except with sides less parallel; it is darker and duller green.

NOTE: The descriptions are composite. That for Black Mitcham (*A*) has been collated from descriptions for *M. piperita officinalis* forma *rubescens* Camus, *M. piperita vulgaris* Sole and *M. piperita β* Smith, and are sufficiently uniform to indicate that these names may be synonymous. Likewise, descriptions for White Mitcham (*B*) have been taken from texts for *M. piperita officinalis* forma *pallescens* Camus, *M. piperita officinalis* Sole, *M. piperita α* Smith and *M. Hudsoniana* Braun.

[38] In Michigan fields, "row mint" is the first-year planting, which is set out in rows and matures later in the season; "meadow mint" represents the second-year crop, in which the row layout is obscured because of the spreading of the plants. Herb and oil yields of the latter are generally considerably greater because there is more vegetative growth per unit area (107).

Tausch var. *Thuringiaca* H. Braun & Topitz[27]. Thuringian oil[28] is inferior to the other German products. It is said that Saxon (Sächsisches Oel)[28] (Miltitz) and Silesian (Schlesisches Oel)[28] (Gnadenfrei) peppermint oils, which are closely similar, are the most expensive and finest known, but they are supplied to the market in very limited amounts (14, 43). They are stated to be superior even to the Mitcham oil, although this does not appear to be a universal opinion. Most German peppermint seems to be near Black Mitcham (43). Oudemans (119) considered the peppermint grown in Holland (*ca.* 1850) to be *M. piperita β officinalis* Koch = subspec. *piperita* Briq.

Pie(d)montese Mint or "Erect Piedmontese" is supposed to be a peppermint somewhat like Mitcham White, which was being cultivated, however, in Italy prior to the introduction of English (Mitcham) peppermint about 1865 (113, 121, 126).

Schinz and Keller (140) note as cultivated in Switzerland the following varieties of *piperita*: *officinalis* Sole, *citriodora* G. F. W. Meyer, *calophylla* Briq. and *hercynica* (Roehl.) Briq.

Cultural forms or races are described or catalogued from time to time, and it is entirely possible that some of these have the meritorious properties often claimed for them. Agricultural research stations sometimes recommend certain strains, usually identifying them by a stock number—thus, by the Sortenregisterstelle in Germany (117) and by agricultural experiment stations in the Soviet Union (*e. g.*, "Hybrid No. 272") (141).

Improved Erfurt or Agnelli's (Improved) Peppermint ("*Mentha piperita Agnelliana*") is said to have been developed by J. Agnelli of Csari, Hungary (132). It was claimed by Rev. Agnelli himself (127) to produce larger and more aromatic leaves, to grow more rapidly and to tolerate a wide range of soils: propagation stock was sold throughout Europe until quite recently (126). Pater (128) after careful trial failed to find it superior. "Var. Eisenstaedtiana" appears to be only a cultural form, although Schuerhoff (129) studied it cytologically.

Attempts have been made at various times to produce once again *Mentha piperita* by artificial crossings of those strains which are thought to have originated the supposed hybrid toward the end of the seventeenth century. Thus, Ruttle (130, 131) raised hybrid seedlings from the putative parents of peppermint, but found that these differed considerably from *M. piperita* in flower, color, hairiness, and in possessing a volatile oil of inferior quality. Hybridization experiments projected at the University of Wisconsin (133, 84) seem never to have materialized.

The failure of efforts to hybridize *Mentha* species to produce a good commercial type of peppermint probably is the resultant of several factors. One of these is the great many varieties of each parent species known[29], with perhaps many more still undescribed, and the number of possible crosses is, of course, tremendously greater. Another difficulty also is the relative sterility of many *Mentha* forms.[30]

Some taxonomists, in dealing with such a complex group as *Mentha*, do not trouble to classify into groups lower than species. Thus, Wiegand and Eames (103) have simplified their study of *M. piperita* by treating it simply as a polymorphic species, in which specimens obtained from various places exhibit wide variability: such as leaves variously narrow or broad, long or short, usually glabrous but occasionally hairy, with inflorescences varying in length and density, and so on.

[27] Var. *drispasmena* Briq. is said to be much cultivated in Switzerland (140).

[28] Commonly known as Deutsches Oel (German Oil); also applied to Saxon.

[29] Thus, Briquet in Engler and Prantl (134) listed 20 varieties of *M. aquatica* L., 16 of *spicata* L. (and indicated more), 14 of *rotundifolia* L. (more indicated), and over 150 of *longifolia* Huds. All of these species are supposed by various geneticists to be progenitors of *M. piperita*.

[30] Ray Nelson (108) noted in peppermint one seedling in about 13,000 flowers.

SUMMARY AND CONCLUSIONS

A study of the nomenclature and subdivisions within *Mentha piperita* has been carried out.

In accordance with the International Rules (143), it would appear proper to designate the species as *M. piperita* L. *pro parte*, Hudson, in place of the customary *M. piperita* L., inasmuch as Hudson's proper identification (1762) preceded that of Linnaeus' emended description (Sp. Pl., 2nd ed., 1763). This is in line with the considered opinion of the most profound students of *Mentha* (J. E. Smith, Bentham, Malinvaud, Briquet).

It is manifest that confusion could be avoided by limiting the vernacular term "peppermint" to *M. piperita* and its varieties, instead of employing the name as broadly as is now done.

Determination of *Mentha* species is found to be frequently in error, and this may at least in part explain the important discrepancies in volatile oil analyses that are so obvious in compilations of these data (138). A recent instance cited here in detail was the misidentification as *M. piperita* of a species in the *M. arvensis* complex. The derived volatile oils had formed the subject of extensive phytochemical studies.

The literature dealing with the classification of *M. piperita* has been reviewed and analyzed to understand better the relationships of economically important subspecific forms.

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Studies in the Pharmacology of Mercury. IV. *In Vitro* Activity of Mercury Dispersion Against *Neisseria Gonorrhoeae**

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The present investigation was undertaken to determine the bactericidal and bacteriostatic activity of a water-soluble mercury emulsion against *Neisseria gonorrhoeae*. This dispersion of metallic mercury, as well as its pharmacological properties, has been described previously (1, 2).

The concentration of mercury in the ointment which was required to kill *N. gonorrhoeae* in twenty minutes was determined on several strains.[1] Tests were carried out at 37°. Tables I, II and III indicate that a 3 per cent concentration of mercury is bactericidal to four strains in twenty minutes, to one strain in thirty, and to one in sixty minutes.

Table IV shows bacteriostatic activity of the 3 per cent mercury dispersion in terms of zone of inhibition on specially prepared agar plates.

EXPERIMENTAL

Bactericidal Tests.—An ointment drop measuring 0.4 to 0.5 cc. was placed in the middle of a sterile petri dish or at the bottom of a Wassermann tube and 0.5 cc. of an overnight culture was thoroughly mixed into the ointment with a glass rod. At the specified intervals one loopful of the mixture was transferred into test tubes containing 5 cc. of enriched media composed of liver extract, hemolyzed horse blood, and 0.1% sodium thioglycollate. This medium is described in detail elsewhere (3). Sodium thioglycollate was prepared from pure thioglycollic acid in this laboratory. Test tubes were kept at 37° for forty-eight hours, then streaked on specially prepared proteose agar plates (3). After forty-eight hours' incubation the plates were read (Tables I–III).

TABLE I.—FOUR STRAINS OF *Neisseria Gonorrhoeae* TREATED WITH A MERCURY DISPERSION IN DIFFERENT CONCENTRATIONS

Strains	Time, Min.	0.1%	0.5%	1%	2%	3%
A	20	+	+	+	+	−
B	20	+	+	+	+	−
C	20	+	+	+	−	−
D	20	+	+	+	+	−

TABLE II.—STRAIN *M* OF *Neisseria Gonorrhoeae* EXPOSED TO VARIOUS CONCENTRATIONS OF A MERCURY DISPERSION AT VARIOUS TIME INTERVALS

Concentrations of Mercury Ointment	Time, Min. 5	10	20	30	60
2%	+	+	−	−	−
4%	+	+	−	−	−
6%	+	+	−	−	−
No mercury	+	+	+	+	+

TABLE III.—BACTERICIDAL ACTIVITY OF A 3 PER CENT MERCURY DISPERSION AGAINST SIX STRAINS OF *Neisseria Gonorrhoeae*

Strains	Time, Min. 1	5	10	20	30	60
A	+	+	+	−	−	−
B	+	+	+	−	−	−
D	+	+	+	−	−	−
E	+	+	−	−	−	−
F	+	+	+	+	+	−
G	+	+	+	+	−	−

Controls, without mercury, all +.

Bacteriostatic Tests.—Enriched proteose agar plates were seeded with *N. gonorrhoeae* and 3% mer-

* Received March 9, 1944, from Wallace Laboratories, Inc., New Brunswick, N. J.
† Present address: Department of Parasitology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md.
‡ Present address: Jewish Hospital, Brooklyn, N. Y.
[1] These were received through the courtesy of Dr. Alfred Cohn, Gonococcus Research Unit, Dept. of Health, New York, N. Y.

cury ointment placed in the center of the plate. Incubation for forty-eight hours at 37° followed, and the zones of inhibition were then measured (Table IV).

TABLE IV.—BACTERIOSTATIC ACTIVITY OF A 3 PER CENT MERCURY DISPERSION AGAINST SIX STRAINS OF *Neisseria Gonorrhoeae*

Strains	Zone of Growth Inhibition	
	No Mercury	Mercury, Mm.
A	0	25
B	0	34
D	0	22
E	0	23
F	0	11.5
G	0	22

DISCUSSION

We have found that a 3 per cent emulsion of metallic mercury possesses marked activity against *N. gonorrhoeae in vitro*. In lower concentrations the bactericidal effect disappears. Early work in the evaluation of mercurials, particularly against *N. gonorrhoeae*, indicated that these drugs were active at very high dilutions (4). Recent investigations using thioglycollate media, however, show that mercurials are not germicidal in high dilution, and that the earlier data were the result of the bacteriostatic effect of mercury, as transferred in the loop to the culture medium (5, 6). Results of *in vitro* studies of mercurials against *N. gonorrhoeae* illustrate this general phenomenon. The clinical failure of mercury in local treatment of gonorrhea lends emphasis to *in vitro* findings. Unpublished studies using the chick embryos also point to the bacteriostatic, rather than bactericidal, nature of mercury.

Sodium thioglycollate, introduced by Brewer (7), inactivates mercury which may be carried over on the loop, and permits true estimation of its *in vitro* activity. On this basis, a re-evaluation of the role of mercurials as antibacterial agents seems necessary. From the work of others cited here, as well as the present studies, it appears that mercury in low concentration is not directly lethal to the common microorganisms, and does not possess rapid antibacterial action either in the test tube or in the clinic.

SUMMARY

1. A water-soluble mercury emulsion as prepared in this laboratory is a powerful bacteriostatic agent against *N. gonorrhoeae*.

2. In concentrations of mercury over 2 per cent, *N. gonorrhoeae* is killed in vitro in from twenty to sixty minutes, depending on the strain present.

3. The antibacterial nature of mercury has been discussed briefly. Our findings indicate that mercury and its compounds are essentially bacteriostatic rather than bactericidal.

REFERENCES

(1) Maren, T. H., and Edwards, B. B., THIS JOURNAL, 32 (1943), 255.
(2) Maren, T. H., Epstein, J. A., and Hand, W. C., *Ibid.*, 33 (1944), 91.
(3) Alture-Werber, E., *J. Bacteriology*, in press.
(4) Swartz, E. O., and Davis, D. M., *J. Urol.*, 5 (1921), 235.
(5) Nungester, W. J., Hood, M. N., and Warren. M. K., *Proc. Soc. Exptl. Biol. Med.*, 52 (1943), 287,
(6) Heineman, B., THIS JOURNAL, 32 (1943), 298.
(7) Brewer, J. B., *J. Am. Med. Assoc.*, 112 (1939), 209.

WHO MAKES IT?

The National Registry of Rare Chemicals, Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago, Ill., seeks information on sources of supply for the following chemicals:

p-Amino hippuric acid
Arachin
1-Amino-4-hydroxy anthraquinone
2-Amino-4-hydroxy anthraquinone
1,2-Benzofluorene
3,4-Benzofluorene
Desoxyribose
N,N-Diethyl carbamic acid ethyl ester
N,N-Diisobutyl dithio carbamic acid (100 Gm.)
7-Dehydro cholesterol
1,8-Dihydroxy anthraquinone
Laccase and related phenol oxidases
2-Methyl-1,2-benzanthracene (0.2 Gm.)
5-Methyl-1,2-benzanthracene (0.2 Gm.)
Pyrazole
Syringaldehyde
2,3,4- or 2,3,5-Trimethyl pyrrole
2,3,4,5-Tetramethyl pyrrole
Yellow enzyme (200 mg.)
Tyrosinase

A Note on the Presence of Calcium Oxalate in the Maya Fruit*

By C. F. Asenjo, J. A. Goyco and M. del C. Fernández†

For the past three years the maya plant (*Bromelia pinguin* L.) has been the subject of study in this laboratory, where preliminary work revealed that the edible part of the maya fruit produced, when chewed, a prickling sensation similar to, though more intense, than that caused by pineapples, a fruit known to contain calcium oxalate. This work also revealed that small but painful ulcers readily developed, within a period of three to six hours, on the fingertips of laboratory workers who handled the pulp of this fruit without rubber gloves.

At first it was thought that these lesions were due only to the digestive action of the pinguinain, a strong proteolytic enzyme present in the fruit (1). Later on, however, one of us was able to produce a small experimental ulcer by simply pressing for about four hours a small piece of the maya pulp on the fleshy tip of a finger. A prickling sensation was immediately felt. This observation led us to suspect that the formation of small ulcers on the fingertips of laboratory workers had been caused not only by the digestive action of the proteolytic enzyme on the tissues but that it was also due to a mechanical irritation produced by the fine needles of calcium oxalate present in the pulp.

The maya fruit is eaten by human beings without any ill effects, producing no lesions of the mouth or on the digestive tract. The only reaction noted so far is a mild irritation around the mouth on the outer part of the lips.

EXPERIMENTAL

Examination of the maya pulp under the microscope.—Figure 1 shows a low power photomicrograph of the maya pulp. A large number of fine calcium oxalate crystals, averaging about 108 μ in length and 5 μ in cross section, are readily visible in the field.

Separation of the needles from the juice.—Five hundred ml. of juice was placed in the icebox for two days. The supernatant liquid was then decanted and the sludge left, found to be rich in fine needles, was mixed with 25 per cent acetic acid, transferred to a bottle and centrifuged. The whitish precipitate obtained was washed several times with 25 per cent acetic acid, then with water, and later dissolved in 10 per cent HCl. This solution was neutralized with NH_4OH and the resulting white crystalline precipitate centrifuged, washed with water, and dried at 100° C.

Fig. 1.—Needles of calcium oxalate in the maya pulp.

TABLE I

	Per Cent Free and Combined Oxalic Acid as $CaC_2O_4 \cdot H_2O$
Whole maya fruit—fresh	0.0838
Whole pineapple—fresh	0.0089
Edible part of wild native taro—fresh	0 1260

Characterization of the crystals.—One-hundredth of a gram of the above crystals was dissolved in 10 per cent H_2SO_4 and titrated with 0.05 *N* $KMnO_4$.

Anal. Calcd. for Ca in $CaC_2O_4 \cdot H_2O$: 27.44; Found 27.62.

In order to confirm the presence of Ca, some of the crystals were dissolved in dilute HCl. When observed with the spectroscope, the flame emitted by this solution showed the characteristic lines for Ca. The needle-like crystals in the maya fruit are, therefore, $CaC_2O_4 \cdot H_2O$.

Quantitative determination of free and combined oxalic acid in the whole maya fruit.—Two hundred grams of whole maya fruit were extracted with 15 per cent HCl by boiling. The mixture was filtered through a Buchner funnel and thoroughly washed with 15 per cent HCl and water; filtrate and washings were then treated by the Majumdar and

* Received June 1, 1944, from the Department of Chemistry of the School of Tropical Medicine of the University of Puerto Rico, under the auspices of Columbia University, and the Agricultural Experiment Station at Rio Piedras, Puerto Rico. A cooperative project.

† We are indebted to Mr. Antonio Puras for the photomicrographs of the crystals.

De (2) method. The oxalates were reported as $CaC_2O_4 \cdot H_2O$.

The contents of free and combined oxalic acid were also determined by this same procedure for both the whole pineapple and the wild native taro, with results as shown in Table I.

SUMMARY

1. The presence of a large number of calcium oxalate needles in the edible portion of the maya fruit has been demonstrated and their average length and diameter measured.

2. The total free and combined oxalic acid in the whole maya fruit, in the pineapple and in the edible portion of wild taro has been determined.

REFERENCES

(1) Asenjo, C. F., and Fernández, M. del C., *Science*, 95 (1942), 48.

(2) Majumdar, B. N., and De, N. K., *Ind. J. Med. Research*, 25 (1938), 671.

United States Pharmacopœial Convention

Activities of the Board of Trustees

The U. S. P. Board of Trustees recently held its annual meeting in New York City, at which time Dr. E. F. Kelly of Washington and Adley B. Nichols of Philadelphia were re-elected as Chairman and Secretary, respectively. While the Board meets at least once annually, shortly after the close of the fiscal year, it conducts its business regularly between meetings through the issuance of Board letters.

Use of U. S. P. Text—During the past fiscal year the Board has passed upon 14 requests for permission to use or refer to U. S. P. text in various publications. Each case is decided upon its own merits, depending upon the amount of text used, the manner in which it is to be presented and the ultimate distribution of the publication involved, and approval may be given without charge or with nominal charges based on the data indicated above.

First U. S. P. XII Bound Supplement.—The Board has had to consider several items relating to the publication of the First U. S. P. XII Bound Supplement, distribution of which was begun in March. This Supplement is being mailed without charge to all holders of copies of the U. S. P. XII, upon receipt of the self-addressed post card order form which is attached to the rear cover of each U. S. P. XII. Certain information is requested on this card, namely, the coupon number of the U. S. P. XII (attached to the rear cover of the title page), the name and mailing address and the signature of sender. Numerous calls have been made through the press to the pharmaceutical and medical professions requesting that the post card orders be mailed promptly. Copies will continue to be distributed as orders are received.

Spanish Edition, U. S. P. XII.—This edition is practically ready for the binder and it is expected that the initial distribution will be made in the near future. Information concerning the edition should be addressed to the distributor, The University Society, 464 Fourth Avenue, New York 16, N. Y.

U. S. P. XIII.—The Board of Trustees has approved the immediate preparation of U. S. P. XIII with the intention that it shall be completed by the close of 1945. This is in keeping with the basic proposal of providing a new Pharmacopœia every five years and will help to bring the revision program into its proper relationship with the revision decade, whereby a new Pharmacopœia shall appear approximately at the close of the fifth and tenth years of the decade. On this basis, a new Revision Committee, appointed at the beginning of a decade, will have full five-year periods for the revision of each edition, each committee completing its task before the beginning of a new decade and the election of a new Committee. The Board recently called for bids for the printing and binding of the U. S. P. XIII, and at their annual meeting awarded the contract to the Mack Printing Company of Easton, Pa.

Reference Standards.—U. S. P. Reference Standards play an important part in serving as controls for many noteworthy preparations, and the Board has been glad to sponsor the preparation of new Standards and maintain the proper stock of all such Standards at all times. Diethylstilbestrol has been added to the list during the past year and it is expected that a group of melting-point Standards will be available in the near future, as well as several new hormone Standards, and a Reference Standard for Penicillin.

Investment of Funds.—As with all new editions of the Pharmacopœia, the initial sale is obviously large, and while most of these receipts must be held to meet expenses for the lean years, the Board hopes to be able to add something to its investment fund with each new edition. At the same time the Board has found it judicious to invest some of the extra

cash, even if only as a temporary measure, in order to profit by the interest which is thus made possible. Accordingly, during the past year the Board invested in one of the more desirable U. S. Treasury Bond Series, and an examination of the current financial report shows a substantial increase in interest received.

Honoraria to the Committee of Revision.—During the past year the Board of Trustees was pleased to be able to vote a very modest honorarium to each member of the Committee of Revision, not by any means as payment for the time and effort spent in preparing the U. S. P. XII, but merely as a small expression of thanks and appreciation for all that was involved. These honoraria will be recognized in the fourth annual financial report which is being issued simultaneously with this report on the Board's activities.

ADLEY B. NICHOLS, *Secretary*

U. S. PHARMACOPŒIAL CONVENTION, WASHINGTON, D. C.

Statement of Income and Expense for the Fourth Year of the 1940–1950 Decennial Period—May 1, 1943, to April 30, 1944

The accounts of the U. S. Pharmacopœial Convention for the year ending April 30, 1944, have recently been audited by the R. G. Rankin Company of Washington and New York, and the Board of Trustees has again authorized the release of the Auditor's Statement of Income and Expense, and the statement of Cash Receipts and Disbursements, together with a supplementary statement covering Revision and Research expenditures.

The income of the Convention is primarily that derived from the sale of Pharmacopœias and it is noted with satisfaction that income for the year again exceeds expense of operation, since it will be recalled that the initial saturation sale of Pharmacopœias occurred during the preceding year, shortly after the release of the U. S. P. XII.

The increase in expense charged to Administration is largely due to the expense for legal counsel required by the Board of Trustees in connection with problems arising at the time of the Cleveland meeting of the Convention in the Spring of 1942. The increase in Revision expenses is accounted for by the honoraria voted to the members of the Revision Committee.

It will be noted that additional U. S. Treasury Bonds were purchased during the year, thus adding to the investments of the Convention, and this added investment is further recognized by the increased income from interest.

As heretofore, the additional breakdown of expenses for Revision and Research is added for general information.

For the U. S. P. Convention
W. PAUL BRIGGS, *Treasurer*

For the U. S. P. C. Board of Trustees,
E. F. KELLY, *Chairman*
ADLEY B. NICHOLS, *Secretary*

STATEMENT OF INCOME AND EXPENSE FOR THE YEAR ENDED APRIL 30, 1944

Income			
Sale of Pharmacopœias:			
Collections		$88,988.72	
Less: Decrease in Accounts Receivable			
April 30, 1943	$27,412.48		
April 30, 1944	9,378.00	18,034.48	70,954.24
Sale of Reference Standards, A. M. A. Articles, etc.:			
Collections		$ 4,231.25	
Add:			
Increase in Collections Pending Remittance to the Treasurer			
April 30, 1944	$ 959.25		
April 30, 1943	274.50		
	$ 684.75		
Collections used to pay Bank Charge	.50	685.25	
		$ 4,916.50	
Less: Decrease in Accounts Receivable			
April 30, 1943	$ 405.59		
April 30, 1944	229.50	176.09	4,740.41

Interest on Investments:			
Collections		$ 2,331.14	
Add: Increase in Accrued Interest Receivable			
April 30, 1944	$ 811.67		
April 30, 1943	546.56	265.11	
		$ 2,596.25	
Less: Accrued Interest Purchased	$ 119.54		
Amortization of Bond Premiums	253.63	373.17	2,223.08
Use of U. S. Pharmacopœia Text by Others			3,085.00
Miscellaneous Income			275.17
Total Income			$ 81,277.90
Less:			
Expenses			
Cost of Publications Sold:			
Publication and Sales Expense	$ 8,844.29		
Add: Decrease in Inventory			
April 30, 1943	$9,503.96		
April 30, 1944	4,836.70	4,667.26	$13,511.55
Administration	$ 5,350.74		
Bank Charge	.50	5,351.24	
Convention		451.28	
Revision:	$31,700.32		
Add: Decrease in Inventory			
April 30, 1943	$1,732.83		
April 30, 1944	1,645.90	86.93	31,787.25
Research		5,877.26	
Stationery and Supplies Inventory Adjustment (minus)		252.56	56,726.02
Excess of Income over Expense			
For the Year ended April 30, 1944			$ 24,551.88

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS (GENERAL ACCOUNT) FOR THE YEAR ENDED APRIL 30, 1944

Cash on Deposit, April 30, 1943		$ 82,062.37
Add:		
Receipts		
Sale of Pharmacopœias	$88,988.72	
Sale of Reference Standards, A. M. A. Articles, etc.	4,231.25	
Interest on Investments	2,331.14	
Use of Pharmacopœia Text by Others	3,085.00	
Miscellaneous	275.17	98,911.28
		$180,973.65

Less:

Disbursements	Publication and Sales	Administration	Convention	Revision*	Research*	Total
Printing & Binding	$8,808.51	$.....	$412.29	$.....	$.....	$ 9,220.80
Honoraria	.....	1,000.00	.....	22,425.00	.....	23,425.00
Clerical	.....	916.00	17.72	4,583.14	137.55	5,654.41
Meetings	.....	171.99	.....	1,603.34	2,007.20	3,782.53
Supplies	.....	34.50	11.27	759.33	681.61	1,486.71
Postage & Telegrams	.....	85.33	10.00	720.65	37.09	853.07
Compensation	.....	.....	.....	.....	2,994.81	2,994.81
Legal	.....	2,792.37	.....	.....	.....	2,792.37
General	35.78	350.55	.....	1,608.86	19.00	2,014.19
	$8,844.29	$5,350.74	$451.28	$31,700.32	$5,877.26	$52,223.89

Add: Purchase of U. S. Treasury Bonds and Accrued Interest	50,400.80	102,624 69
Cash on Deposit, April 30, 1944		$ 78,348.96

A MORE DETAILED AND SUPPLEMENTARY FINANCIAL STATEMENT OF THE REVISION EXPENSES MAY 1, 1943, TO APRIL 30, 1944

REVISION—MEETINGS

Open hearing on First U. S. P. XII Bound Supplement	$ 689.84
Conferences on establishment of new Digitalis Assay Reference Standard	160.74
Traveling, hotel, and incidental expenses of Revision Chairman, and special committee groups for various conferences and meetings relating to or required by the revision program. Included are approximately 17 Washington conferences, 14 at New York, 1 each at Detroit, Chicago, Baltimore and Hot Springs, and several chemical conferences regarding text for the First Bound Supplement	752.76
	$1,603.34

REVISION—SUPPLIES

Stationery	$ 178.55
Mimeograph supplies	258.03
Pituitary Reference Standard	97.60
Miscellaneous office supplies, maintenance on 4 typewriters, reprints, floral tributes, etc.	225.15
	$ 759.33

REVISION—CLERICAL

Stenographic and clerical assistance through Chairman's office	$4,583.14

REVISION—POSTAGE AND TELEGRAPH

Postage, express, telephone and telegraph service	$ 720.65

REVISION—GENERAL EXPENSES

Reference Standards—preparation, renewal and maintenance, including Diethylstilbestrol, Nicotinic Acid, Insulin, Posterior Pituitary, Ascorbic Acid, Digitalis, Melting Points	$ 503.33
Contribution to AMERICAN PHARMACEUTICAL ASSOCIATION toward publication of Pharmaceutical Abstracts	1000.00
Inter-Society Color Council	25.00
Miscellaneous	80.53
	$1,608.86

REVISION—SALARIES AND HONORARIA

Honoraria to members of Revision Committee:	
H. G. Barbour	$ 100.00
Walter Bastedo	700.00
George D. Beal	1,200.00
Francis E. Bibbins	500.00
Charles L. Brown	200.00
Joseph B. Burt	100.00
W. B. Castle	500.00
C. W. Chapman	200.00
B. V. Christensen	300.00
Arthur C. De Graff	100.00
M. S. Dooley	100.00
Carl A. Dragstedt	100.00
A. G. Dumez	500.00
Mrs. C. W. Edmunds, for Dr. Edmunds	100.00
Cary Eggleston	100.00
Robert P. Fischelis	*100.00
P. A. Foote	100.00
Harry Gold	400.00
Forest J. Goodrich	100.00
Loyd E. Harris	100.00
Thomas J. Hill	100.00
M. L. Jacobs	100.00
Glenn L. Jenkins	300.00
Mrs. C. B. Jordan, for Dr. Jordan	500.00
John C. Krantz, Jr.	800.00
H. A. Langenhan	300.00
Mrs. J. Leon Lascoff, for Dr. Lascoff	100.00
C. O. Lee	100.00
A. B. Lemon	100.00
Perrin H. Long	100.00
E. K. Marshall	100.00

George W. McCoy	500.00
W. L. Mendenhall	100.00
Hugh C. Muldoon	200.00
E. E. Nelson	700.00
E. L. Newcomb	200.00
C. Leonard O'Connell	100.00
Justin L. Powers	100.00
J. Allen Reese	100.00
Leon W. Richards	100.00
Joseph Rosin	1,000.00
George C. Schicks	100.00
Carl L. A. Schmidt	100.00
A. John Schwarz	100.00
Leonard A. Seltzer	500.00
Virgil A. Simpson	100.00
Isaac Starr	100.00
Frank O. Taylor	500.00
Mrs. Soma Weiss, for Dr. Weiss	500.00
Elmer H. Wirth	300.00
Heber W. Youngken	500.00
Louis C. Zopf	100.00
Salary:	
Revision Chairman, E. Fullerton Cook	5,700.00
Executive Assistant to Chairman, Adley B. Nichols	2,625.00
	$22,425.00

* Dr. Fischelis returned his check to the Convention.
* A more detailed statement will be found on the following pages.

RESEARCH

Subcommittee		Meetings, Supplies Postage, Clerical Travel and General	Technical Assistance	
3—Biological Assays		$ 10.00		
5—Botany & Pharmacognosy		75.07	Asst. to Dr. Youngken	$ 25.00
7—Inorganic Chemicals		50.71	Dr. F. K. Bell, Asst. to Dr. Krantz, Salary	$1,444.81
8—Organic Chemicals		1,000.00	Miss Eleanor Sackter and Mr. Kenneth Waters, Asst. to Dr. Beal, Salary	$1,350.00
Clerical	$ 20.00			
Supplies	598.00			
Meetings	375.00			
Post. & Tel.	7.00			
13—Ointments		290.18	Mr. Fred Landon, Asst. to Prof. Zopf	$ 125.00
Meeting	$284.08			
Clerical	5.10			
Post. & Tel.	1.00			
Hormone Board Meeting		710.23		
Vitamin Board		111.36	Dr. O. L. Kline, Analysis of B Assay Study	$ 50.00
Meeting	$107.36			
Misc.	4.00			
Anti-anemia Board		447.29		
Clerical	$ 80.00			
Supplies	11.40			
Meeting	342.92			
Post. & Tel.	12.97			
Digitalis Assay Committee Meeting		75.93		
Penicillin Conference		111.68		
		$2,882.45		$2,994.81
				2,882.45
Total				$5,877.26

Book Reviews

A Source Book of Agricultural Chemistry, by CHARLES A. BROWNE. Chronica Botanica Co., Waltham, Mass.; G. E. Stechert and Co., New York, N. Y., x + 290 pp., 17.5 x 26 cm. Price, $5.00.

This is one of the rare books the extraordinary scope and meaning of which have not been and apparently could not be covered adequately by title. It is far more than "A Source Book of Agricultural Chemistry." It is a documentary history of the change of chemical concepts within agriculture, and it touches in its travel from Graeco-Roman antiquity to the period initiated by Justus von Liebig, an almost incredible variety of subjects and ideas. Beneath the chapters forming this book and the judgments contained in it, lies an enormous amount of searching, reading, reflection and discernment.

The method employed by Charles A. Browne is a bio-bibliographical one. Brief but pertinent biographies of the authors quoted are followed by extracts from their writings, and both authors and quotations are presented in relation to the world in which they lived and to posterity, offering much essential information for every one interested in the development of science and of human thought.

The author starts with an introduction defining the phrase "agricultural chemistry" as "a conventional term" meaning "the chemistry of farm operations" and deals with this subject proper in seven chapters devoted to agricultural chemistry in ancient times (I), in the alchemical and iatrochemical periods (II), in the time of the early royal society (III), in the early phlogiston period (IV), in the late phlogiston period (V), during the chemical revolution (VI) and at the beginning of the modern period (VIII). The book closes with an "addendum" containing references to, and an excellent classification of books on the history of chemistry written in the century 1840–1940. The following notes are of a supplementary rather than of a critical character.

In Chapter I Browne mentions the first Latin translation of the "Materia Medica" of Dioscorides and quotes from Wellman's Latin edition (1907–1914) in an English translation of his own. It may be of interest to the reader that there exists an English translation prepared by John Goodyear in 1655 and edited by Robert T. Gunther (Oxford, 1934). A translation from the Greek original into German with numerous annotations representing a thorough pharmaceutico-chemical comment was published by the pharmacist J. Berendes under the title "Des Pedanios Dioskurides Arzneimittellehre" (Stuttgart, 1902).

As to the excellent discussion of the religious and general ideological concepts dominating the work of the great naturalists of the sixteenth and early seventeenth centuries or at least determining their way of building up and expressing their scientific hypotheses (Part II), the reader will find additional material especially as far as Paracelsus and Van Helmont are concerned in Walter Pagel's *The Religious and Philosophical Aspects of Van Helmont's Science and Medicine* (Baltimore, 1944). The famous story of Paracelsus' "break with tradition by burning the books of Galen and Avicenna before his students" (p. 22) is now thought to be an invention of later days. There could not be found any contemporary evidence for this demonstrative act. So to stay in parentheses, the little-known fact may be mentioned that it was an apothecary, Melchior Dorss, owner of the pharmacy in Kolmar, to whom the world is indebted for the preservation of some of the manuscripts of Paracelsus ("Acta Paracelsica," 1 (1930), 32).

The eminent part played by pharmacists in the development of scientific chemistry becomes evident throughout the parts of Browne's book dealing with this period, especially the chapters IV to VIII. The author devotes seven pages (157–163) to the work of Carl Wilhelm Scheele and he stresses the fact that "like many other famous chemists he began his career as a pharmacist and he continued as such until his death." The readers of this journal are naturally interested to know which other pharmacists are mentioned by Browne in connection with the development of agricultural chemistry before Liebig, be it with or without special reference to their belonging to or coming from pharmacy. There is first of all Andreas Sigismund Marggraf (1709–1782), the famous discoverer of sugar in the beet. Following incomplete and even incorrect statements in H. Kopp's *Geschichte der Chemie*, Browne reports "that his father was a Berlin pharmacist under whom the son acquired his first training in chemistry." The pharmaceutical world thinks this son of a pharmacist to have been himself a pharmacist long enough to be claimed by the profession. Having worked in the pharmacy of his father besides attending school, A. S. Marggraf went through a regular five years' apprenticeship (1725–1731) in the Royal Prussian Court Pharmacy managed by the renowned apothecary chemist Caspar Neumann. He worked as a clerk first in the pharmacy of the apothecary Rössler at Frankfurt on the Oder and then in the *Hirschapotheke* at Strassburg owned by the apothecary Johann Jacob Spielmann. It was not until 1733, *i. e.*, after eight years of practicing pharmacy, that he devoted himself exclusively to academical studies which he pursued at the University of Halle and at the Mining School of Frieberg. From 1735 he became an assistant to his father, doing pharmaceutical as well as research work until his being appointed a member of the Prussian Academy of Sciences in 1738.

Browne states that Lavoisier obtained his first chemical training by G. F. Rouelle (1703–1770). Guillaume François Rouelle, called "Rouelle l'ainé," was an apothecary who, besides being a lecturer at the Jardin du Roi in Paris and a member of the French Royal Academy of Sciences, conducted a pharmacy until his death. Of "the celebrated French chemist," J. A. C. Chaptal (1756–1832), Browne states that he "was born the son of an apothecary, at Nogaret in the department of Lozère in southeastern France." Chaptal, an eminent statesman as well as chemical technologist, had no connection whatsoever with pharmacy except the fact of his being born in a pharmacy.

The importance of the work of the apothecary Sigismund Friedrich Hermbstädt (1760–1833), who besides his comprehensive teaching and writing practiced pharmacy for about twenty years, has found ample recognition (pp. 189–192). The author mentions Hermbstädt's translation of the works of Lavoisier into German. It is of interest that it was the same man who, in 1793, edited for the first time the collected papers of Carl Wilhelm Scheele.

"The French chemist," Henri Braconnot (1780–1855), to whom Browne refers several times, practiced pharmacy at Strassburg previous to his appointment to a professorship at Nancy (Kremers-Urdang, "History of Pharmacy," p. 348). On page 221 Browne mentions a man by the name of Schrader who "was awarded a prize by the Berlin Academy of Sciences in 1799 for two papers which he published upon the generation of mineral constituents in different domestic grains." It was the apothecary Johann Christian Karl Schrader (1762–1826),

owner of a pharmacy in Berlin, whose erroneous conclusion "that mineral matter was actually created in the plant" was thus honored. The final refutation of this centuries-old error came likewise from the side of pharmacy. The fundamental publication on the inorganic constituents of plants (1842) which proved "beyond all possibility of doubt" that these constituents are not products of the vital activity of the plants but derived entirely from without (pp. 220–225), had as its authors "A. F. Wiegmann, a professor of Brunswick, and L. Polstorff, an apothecary of the same city" or, as these men called themselves on the title page of their brochure, "Dr. A. F. Wiegmann, Professor in Braunschweig und L. Polstorff, Administrator der Hofapotheke [court pharmacy] in Braunschweig." In fact, both men came from pharmacy, and it is in his capacity as a pharmacist that A. F. Wiegmann has been mentioned in J. C. Poggendorff's "Biographisch-Literarisches Handwörterbuch zur Geschichte der exakten Wissenschaften" and in the note about his death in *Archiv der Pharmacie*, 1853. The apothecaries A. E. Wiegmann and Louis Polstorff were, by the way, awarded a prize by the same Berlin Academy of Sciences that about forty years ago had honored the apothecary Schrader in the same way for his erroneous work.

Of the other five scientists named by Browne as remarkable participants in the discussion concerned during the first half of the nineteenth century, Jean Louis Lassaigne—not Lessaigne—(1800–1859) was likewise a pharmacist while Wilhelm August Lampadius (1772–1844) had started his career in going through a pharmaceutical apprenticeship. A successfully accomplished pharmaceutical apprenticeship was likewise the basis of the career of Jean Baptiste Dumas (1800–1884), the great French counterpart of Liebig in senseful scientific work as well as in senseless nationalistic claims, while Justus von Liebig (1803–1873) stayed with pharmacy only for ten months, too short a time to claim him for pharmacy but long enough to make him pharmacy conscious and a lifelong friend of pharmacy and pharmacists. Browne mentions that "Liebig, by means of the reliable methods of ash analysis devised in his laboratory by Will and Fresenius, came to have a much more accurate knowledge of the mineral matter of crops than was possessed by De Saussure, or Sprengel." Heinrich Will (1812–1890) and also Carl Remigius Fresenius (1818–1897) were accomplished pharmacists when they decided to study with Liebig. The part played by pharmacists in Liebig's famous laboratory at the University of Giessen is drastically evidenced by the fact that in a contest Liebig offered to his students in 1835, nine of the ten prize winners were pharmacists.

In his Addendum at the end of his excellent book, Charles A. Browne mentions the late Edward Kremers' "Introduction to Phytochemistry" (Madison, Wis., 1931) among the publications which he thinks to be or to contain "excellent historical introductions" into the study of agricultural chemistry. There is undoubtedly some similarity between the man paying this tribute and the man to whom it is paid. Both belonged to the pioneers in their respective fields in the United States. Both had studied abroad and received their doctorates at the same University, Goettingen. To both of them science has at no time meant merely the arrival at some knowledge and the ability of using this knowledge for some practical purpose. To both of them it always has been a way to make life as such more purposeful, sensible and worth while. It is understood that in this way both men of necessity became historians and that the final goal in their historical work has been that last and most refined understanding based on wisdom.

This review cannot be concluded without a few words about the publishers of this volume. Established in Holland in 1935 as "the International Plant Science Newspaper" and fallen victim of the German invasion of the Low Countries, the *Chronica Botanica* was revived in October, 1940, in these United States of America by their courageous editor, Dr. Frans Verdoorn. Simultaneously a special botanical publishing house was founded for the issuance not only of this journal but of other botanical publications also. In the short time of its existence the Chronica Botanica Co., Waltham, Mass., has published a whole series of botanical books of special as well as of general interest. It has created not only recognition and respect for itself and its capable editor, but has proved to fill a gap within the scientific life of the English-speaking world.—GEORGE URDANG.

Intravenous Anesthesia, by R. CHARLES ADAMS. Paul B. Hoeber, New York, 1944. XIV + 663 pp. 75 illus. 15 x 23.5 cm. Price $12.00.

Basically this book is intended for surgical anesthetists, but it has appeal for research-minded and well-informed pharmacists.

The first four chapters discuss the history of intravenous anesthesia, general techniques and a comparison of the different drugs used for this purpose. The following 22 chapters are concerned with the individual drugs. Two additional chapters have been added on analeptics and the "Use of Barbiturates in Military Surgery."

The chapters on the individual drugs are the most appealing to the pharmacist. The patterns of these chapters are similar and characterized by a brief discussion of the chemistry and a detailed account of the pharmacology and clinical application. The chemistry, as one would expect from the avowed function, is inclined to be superficial. It is more complete when discussing more widely used drugs as pentothal and amytal. The pharmacology is complete as far as the literature—especially American literature—is concerned. Occasionally important phases of the pharmacology have been omitted. Such a case is the failure to mention the capillary toxicity of barbital. While the pharmacology sections are reasonably complete from a documentary standpoint, they often leave something to be desired from an interpretive viewpoint.

A few typographical errors and examples of poor phraseology occasionally detract. For example, on page 90 "ethyl" is misspelled "ethel" in glaringly large type. On page 141 "methyl" is defined as an atom group. Ethyl is spoken of as a univalent alcohol radical and butyl as a hydrocarbon radical in such a manner as to imply two distinct types of radicals.

Professional minded pharmacists, research chemists interested in the relationship between structure and function in this series, and pharmacologists as well as professional anesthetists will find this book worthy of a place on their shelves.—M. W. GREEN.

Synopsis of Materia Medica, Toxicology, and Pharmacology, by FORREST RAMON DAVISON. C. V. Mosby Company, St. Louis, 1944, 3rd ed. 759 pp., 40 illus. 12 x 16 cm. Price $6.50.

This is the third edition of a well-established text in pharmacology. The new edition maintains the same basic form as previous editions but the author has added new information on new sulfonamides, B complex vitamins, vitamin K, the hormones and anti-infective drugs. The chapter on toxicology has been enlarged.

The reviewer still objects to the use of analeptic drugs to treat morphine poisoning, since morphine is biphasic in its action and animal experimentation has clearly indicated it to be dangerous.

The same failure to give pertinent pharmacological data is evident in this edition as in former ones. Demerol might be cited as a case in point. Although a new drug, there is an appreciable quantity of information available in the medical and pharmacological literature on the subject. It is therefore difficult to justify the dismissal of this drug in three short paragraphs which emphasize the spasmolytic action and summarize the analgesic activity by terming it a sedative which can be as satisfactory a preanesthetic as morphine.—M. W. GREEN.

Experimental Spectroscopy, by RALPH A. SAWYER, University of Michigan. Prentice-Hall, Inc., New York, 1944. viii + 323 pp., 107 figures, 20 tables. 16 x 23.5 cm. Price $5.00.

As stated by Professor Sawyer in the first paragraph of the preface, "The purpose of this book is to discuss prism and grating spectrographs and the techniques of their use in research. It is designed for students of spectroscopy and for those in research laboratories who wish to make use of spectroscopic procedures. For this reason, extensive mathematical treatments have been avoided; a background of general physics and some physical optics should be sufficient for an understanding of the presentation."

It is the author's aim, as outlined above, to discuss the fundamental principles, theories and uses of spectrographic equipment. The main subject is prefaced with a brief history of spectroscopy followed by a detailed discussion of light sources with suggestions for their use. The next five chapters covering the General Principles, Theory and Construction, Types and Uses of Spectrographs, Theory and Production, and Mounting and Use of Gratings are splendid and sufficient. Other parts of the book lack details and practical suggestions on actual application, but these chapters are adequate for a textbook or a laboratory reference manual. A prospective photographer might well study Chapter 8 on the Photographic Process since many of the problems of types and characteristics of photographic emulsions as well as a good description of wave-length sensitivities of the different emulsions are discussed. Chapters 9 and 10 on The Determination of Wave Length and Determination of Spectral Intensity are excellent and the description of microphotometers is especially good. The three remaining chapters (Infrared, Vacuum Ultraviolet Spectroscopy, and Spectrochemical Analysis) are useful but disappointing in their lack of detail. The developments in infrared spectroscopy are advancing so swiftly that any treatise on this subject is incomplete before it leaves the printer.

It is a pleasure to read a book so concisely and interestingly written. One is immediately impressed by the absence of padding and the carefully selected bibliography. The printing is clear, the diagrams are sharp and the paper is remarkably good for wartime. As a text and reference book for students and research workers this book is very valuable but it is less useful to one engaged in applied spectroscopy. Considering the small size of the volume, several chapters might well have been added describing the applications of spectroscopic procedures in research and industry.—K. L. KELLY

The Analytical Chemistry of Industrial Poisons, Hazards and Solvents, by MORRIS B. JACOBS. Interscience Publishers, New York, 1944. xviii + 660 pp., 15 x 23 cm. Price $7.00.

The importance of hygiene in modern industry is reflected in the number of books available in the field. The books, however, have been limited largely to the medical, pathologic and toxicologic applications. This makes a reference which is chemically oriented doubly significant.

The first four chapters of this book deal with methods of sampling, determination of gas concentrations and similar general considerations. These chapters are followed by two chapters on dust and silica determinations. The remainder of the book is given over to the analytical determination of the metals, acids and organic substances as industrial hazards. While the emphasis in these sections is naturally upon industrial hygiene, the analytical and pharmaceutical chemist will find the well-documented discussions of specific analytical methods helpful in their fields. Many of these substances are of pharmaceutical interest, as, for example, tetrachlorethylene, carbon tetrachloride, isopropyl alcohol, ether, the glycols, ethyl acetate, nitroglycerin and phenol.

Pharmacologists and toxicologists will find a limited amount of data such as the threshold concentrations of chlorinated hydrocarbons found to be toxic to cats. But it must be emphasized that this book is intended to be chemically oriented.

This book should be on the reference shelves of every college of pharmacy and reference library in the pharmaceutical industry.—M. W. GREEN.